



POWER OF ATTORNEY

#10

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

**In re:** U.S. Patent No. 6,589,508  
**Inventors:** Aberg *et al.*  
**Issued:** July 8, 2003  
**Atty Dckt No.:** 4821-604-999  
(CAM 208423-600008)  
**Assignee:** Sepracor Inc.  
**For:** Methods and Compositions for Treating  
Pulmonary Disorders Using Optically Pure  
(R,R) Formoterol

**POWER OF ATTORNEY**

Mail Stop Post Issue  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Sepracor Inc. (assignee) hereby appoints:

☒ Practitioners at Customer Number 20583

as his/her/its/their attorney(s) or agent(s) to prosecute the Application for Extension of Patent Term Under 35 U.S.C. § 156 filed herewith in connection with the above-identified patent.

Please direct all correspondence in connection with the Application for Extension of Patent Term Under 35 U.S.C. § 156 filed in connection with the above-identified patent to:

☒ The above mentioned Customer Number.

☒ Firm or Individual Name:

Address: Jones Day, 222 East 41st Street, New York, New York 10017

Telephone: (212) 326-3939

Sepracor Inc. is the:

- ☐ Applicant/Inventor  
☒ Assignee of record of the entire interest. See 37 CFR 3.71.  
(Statement under 37 CFR 3.73(b) is applicable)

**Statement Under 37 C.F.R. 3.73(b)**

Sepracor Inc. states that it is:

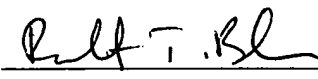
- ☒ the Assignee of the entire right, title, and interest; or  
☐ an assignee of less than the entire right, title and interest.  
The extent (by, percentage) of its ownership interest is %

1. The above-identified application is a continuation of U.S. Application No. 09/535,200, filed March 27, 2000, now U.S. Patent No. 6,299,863, which is a continuation of U.S. Application No. 09/136,109, filed August 18, 1998, now U.S. Patent No. 6,068,833, which is a continuation of U.S. Application No. 08/613,382, filed March 7, 1996, now U.S. Patent No. 5,795,564. An assignment in connection with U.S. Application No. 08/613,382 from Gunnar Aberg and John Morley to Sepracor Inc. was recorded in the United States Patent and Trademark Office on July 5, 1996 at Reel 008018 / Frame 0813.

☐ Additional documents in the chain of title are listed on a supplemental sheet.

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

**ASSIGNEE: Sepracor Inc.**

Date: 29<sup>th</sup> November, 2006 Signature:   
Typed Name: Robert T. Barker  
Position/Title: Assistant Secretary

Note: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required.

ROBERT T. BARKER  
ASSISTANT SECRETARY  
SEPRACOR INC



Express Mail: EB 083401548 US

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**In re:** U.S. Patent No. 6,589,508 **Attorney Docket No.:** 4821-604-999  
(CAM: 208423-600008)  
**Issued:** July 8, 2003  
**Inventors:** Aberg *et al.*  
**Assignee:** Sepracor Inc.  
**For:** Methods and Compositions for  
Treating Pulmonary Disorders  
Using Optically Pure (R,R)  
Formoterol

**MAIL STOP PATENT EXTENSION**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**FEE TRANSMITTAL LETTER**  
**FOR AN APPLICATION FOR EXTENSION UNDER 35 U.S.C. § 156**

Sir:

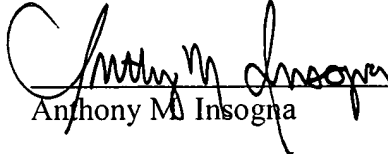
Transmitted herewith is an Application for Extension of Patent Term Under 35 U.S.C. § 156 for U.S. Patent No. 6,589,508, accompanied by two additional copies. The undersigned attorney for Applicant hereby states that these copies are certified to be duplicates of the original. Each copy contains the following exhibits:

Exhibit A	U.S. Patent No. 6,589,508
Exhibit B	Assignment Recordation & Assignment
Exhibit C	Approved Product Label
Exhibit D	FDA Approval Letter
Exhibit E	Terminal Disclaimer
Exhibit F	Maintenance Fee Payment Record
Exhibit G	Compendium of Significant Regulatory Activities in Connection with BROVANA <sup>TM</sup> IND and NDA

Please charge the required fee estimated to be \$1,120.00 to Jones Day Deposit Account No. 50-3013. The Director is hereby authorized to charge any additional fees, which may be required, or credit any overpayment to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: December 1, 2006

 35,203  
Anthony M. Insogna (Reg. No.)

**JONES DAY**  
222 East 41<sup>st</sup> Street  
New York, NY 10017  
(212) 326-3939



Express Mail: EB 083401548 US

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**In re:** U.S. Patent No. 6,589,508

**Attorney Docket No.:** 4821-604-999  
(CAM: 208423-600008)

**Issued:** July 8, 2003

**Inventors:** Aberg *et al.*

**Assignee:** Sepracor Inc.

**For:** Methods and Compositions for  
Treating Pulmonary Disorders  
Using Optically Pure (R,R)  
Formoterol

**MAIL STOP PATENT EXTENSION**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**APPLICATION FOR EXTENSION OF PATENT TERM  
UNDER 35 U.S.C. § 156**

Sir:

In accordance with 35 U.S.C. § 156 and 37 C.F.R. § 1.740, Sepracor Inc., through the undersigned, represents that it is the owner of record of United States Patent No. 6,589,508 ("the '508 patent"), attached hereto as Exhibit A, and hereby requests an extension of the patent term thereof. A copy of the assignment and assignment recordation from the United States Patent and Trademark Office ("USPTO") for U.S. Patent No. 5,795,564, which is the great grandparent of the '508 patent, and which was recorded at Reel 8147, frame 0954, confirming that all right, title, and interest resides in Sepracor Inc., is attached hereto as Exhibit B.

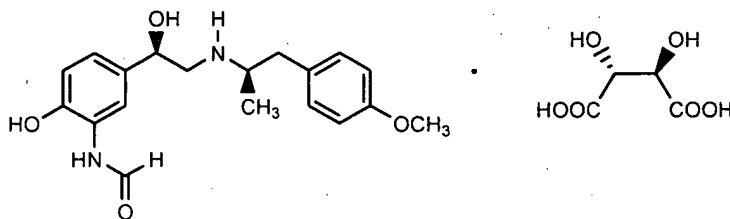
The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740. The sections of this application are numbered in a manner corresponding with the numbering of subparagraphs (1) to (15) of 37 C.F.R. § 1.740(a) and follow the format set forth therein.

12/05/2006 SDENB0B1 00000042 503013 6589508  
01 FC:1457 1120.00 DA

12/05/2006 SDENB0B1 00000040 503013 6589508  
01 FC:1253 1020.00 CR  
12/05/2006 SDENB0B1 00000040 503013 6589508  
01 FC:1253 1020.00 CR

(1) "A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics."

The approved product is BROVANA<sup>TM</sup>, the active ingredient of which is arformoterol tartrate. A chemical name of arformoterol tartrate is formamide, N-[2-hydroxy-5-[(1R)-1-hydroxy-2-[[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]- (2R,3R)-2,3-dihydroxybutanedioate (1:1 salt), and the structure is shown as below:



Synonyms for arformoterol include "the (R,R)-enantiomer of formoterol," "(R,R)-isomer of formoterol," or "(R,R)-formoterol." The molecular weight of arformoterol tartrate is 494.5 g/mol, and its empirical formula is  $C_{19}H_{24}N_2O_4 \cdot C_4H_6O_6$ . (See Product Label at Exhibit C, page 1, lines 24-25).

As currently approved, BROVANA<sup>TM</sup> is indicated for the long-term maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease ("COPD"), including chronic bronchitis and emphysema. (See Product Label, page 8, lines 283-286). Currently, the approved product is available in the form of an inhalation solution, 15 mcg/2 mL (arformoterol; equivalent to 22 mcg of arformoterol tartrate), for oral inhalation. (See Product Label at Exhibit C, page 19, lines 631-633).

***(2) "A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred."***

BROVANA<sup>TM</sup> was subject to regulatory review for an investigational new drug application ("IND") and a new drug application ("NDA") under section 505 of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355 ("FFDCA"). Section 505(b) of the FFDCA, 21 U.S.C. §355(b), authorizes the filing of an NDA for a new drug. The Food and Drug Administration ("FDA") subsequently approved the BROVANA<sup>TM</sup> NDA (21-912) under the authority granted by section 505(c) of the FFDCA, 21 U.S.C. § 355(c).

***(3) "An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred."***

BROVANA<sup>TM</sup> received permission for commercial marketing or use by the FDA pursuant to section 505(b) of the FFDCA, 21 U.S.C. § 355(b), on October 6, 2006. Copies of the Product Label and FDA Approval Letter are attached as Exhibits C and D, respectively.

***(4) "In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved."***

The active ingredient in BROVANA<sup>TM</sup> is arformoterol tartrate. Arformoterol tartrate has not been previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act or the Virus-Serum-Toxin Act.

***(5) "A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the last day on which the application could be submitted."***

This application is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. § 1.720(f), the last day for said submission being December 4, 2006.

***(6) "A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration."***

The complete identification of the patent for which extension is sought is as follows:

Inventors:	Gunnar Aberg and John Morley
Patent No.:	6,589,508
Issue Date:	July 8, 2003
Expiration Date:	April 3, 2012

***(7) "A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings."***

A copy of U.S. Patent No. 6,589,508 ("the '508 patent"), for which this extension is sought, is attached hereto as Exhibit A.

***(8) "A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certificate issued in the patent."***

A copy of the terminal disclaimer filed December 5, 2002, which disclaims the terminal part of the '508 patent extending beyond the expiration of U.S. Patent No. 5,795,564, is attached hereto as Exhibit E.

No reexamination certificate for the '508 patent was issued.

A copy of the 4<sup>th</sup> year maintenance fee receipt is attached hereto as Exhibit F; thus, no maintenance fee is currently due. The 8<sup>th</sup> year maintenance fee is not due until 2010.



**(9) “A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on: (i) The approved product, if the listed claims include any claim to the approved product; (ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and (iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product.”**

The ‘508 patent claims, *inter alia*, a method of using the active ingredient of the approved product BROVANA<sup>TM</sup>. More specifically, at least independent claims 7 and 13 of the ‘508 patent, and at least dependent claims 8-9 and 14-15, claim methods of using the active ingredient of the approved product. Exemplary claims are set forth below:

Claim 7

A method of treating or preventing bronchospasm in a human, the method comprising administering to the human a therapeutically effective amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight of (S,S)-formoterol, or a pharmaceutically acceptable salt thereof.

Claim 13

A method of eliciting bronchodilation effect in a human, the method comprising administering to the human a therapeutically effective amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof.

The Product Label for the approved product states that BROVANA<sup>TM</sup> is indicated for the long term maintenance treatment of bronchoconstriction. (See Product Label at Exhibit C, page 9, lines 283-285). The Product Label also indicates that, in clinical trials, administration of BROVANA<sup>TM</sup> resulted in significantly greater post-dose bronchodilation compared to placebo. (See Product Label at Exhibit C, page 7, lines 258-261). Thus, claims 7 and 13 claim methods of using the approved product.

The Product Label for the approved product states that the recommended dose of BROVANA<sup>TM</sup> for COPD patients is 15 microgram administered twice daily by nebulization. (See Product Label, page 18, lines 608-610). Thus, at least dependent claims 8-9 and 14-15 also claim methods of using the approved product.

***(10) "A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:***

***(i) For a patent claiming a human drug, antibiotic, or human biological product:***

***(A) The effective date of the investigational new drug (IND) application and the IND number;***

***(B) The date on which a new drug application (NDA) or a Produce License Application (PLA) was initially submitted and the NDA or PLA number; and***

***(C) The date on which the NDA was approved or the Product License issued."***

The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period for BROVANA<sup>TM</sup> are as follows:

(a) Investigational new drug ("IND") application number 55,302 was received by the FDA on February 24, 1998 and became effective on March 26, 1998, which is 30 days after the receipt of the IND by the FDA.

(b) The new drug application ("NDA") was submitted on December 8, 2005, and was later assigned NDA number 21-912.

(c) NDA number 21-912 was approved by the FDA on October 6, 2006 (Exhibit D).

***(11) "A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities."***

A chronology of selected regulatory activities is attached hereto as Exhibit G to briefly describe certain activities undertaken with respect to the approval of BROVANA<sup>TM</sup> during the applicable regulatory review period and the dates applicable to such activities.

***(12) "A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined."***

Applicant is of the opinion that the '508 patent is eligible for an extension and estimates the extension to be 745 days, the calculation of which is described below.

A. Eligibility:

(a) Pursuant to 35 U.S.C. § 156(a), the '508 patent claims a method of using the active ingredient;

(b) Pursuant to 35 U.S.C. § 156(a)(1), the term of the '508 patent has not expired before submission of this application for extension;

(c) Pursuant to 35 U.S.C. § 156(a)(2), the term of the '508 patent has never been extended;

(d) Pursuant to 35 U.S.C. § 156(a)(3), the application for extension is submitted by the owner of record of the '508 patent;

(e) Pursuant to 35 U.S.C. § 156(a)(4), the approved product, BROVANA<sup>TM</sup>, has been subject to a regulatory review period before its commercial marketing or use;

(f) Pursuant to 35 U.S.C. § 156(a)(5), the permission for the commercial marketing or use of BROVANA<sup>TM</sup> after the regulatory review period is the first permitted commercial marketing or use of this product;

(g) Pursuant to 35 U.S.C. § 156(c)(4), no other patent has been extended for the same regulatory review period for the approved product BROVANA<sup>TM</sup>.

B. Regulatory Review Period:

(a) Pursuant to 37 C.F.R. § 1.775(c)(1), the period from March 26, 1998 (the date IND application number 55,302 became effective) to December 8, 2005 (the date the NDA was initially submitted) is 2,815 days. Accordingly, Applicant calculates the "Testing Phase" as 2,815 days.

(b) Pursuant to 37 C.F.R. § 1.775(c)(2), the period from December 8, 2005 (the date the NDA was initially submitted) to October 6, 2006 (the date of NDA approval) is 303 days. Accordingly, Applicant calculates the “Approval Phase” as 303 days.

C. Extended Patent Term:

(a) The number of days in the regulatory review period which were on and before July 8, 2003, the date on which the ‘508 patent issued, is 1,931 days. Accordingly, 1,931 days are subtracted from the regulatory review pursuant to 37 C.F.R. § 1.775(d)(1)(i). Thus, Applicant calculates the “Adjusted Testing Phase” to be 884 days.

(b) As demonstrated in Exhibit G, the Applicant acted with due diligence during the regulatory review period. Accordingly, zero (0) days are subtracted from the regulatory review period pursuant to 37 C.F.R. § 1.775(d)(1)(ii).

(c) One half of the number of days remaining in the Testing Phase after the above reductions is 442 days. Accordingly, 442 days are subtracted from the regulatory review period pursuant to 37 C.F.R. § 1.775(d)(1)(iii).

(d) The period remaining in the term of the patent (set to expire April 3, 2012) measured from the date of approval of BROVANA™ (October 6, 2006) (2,007 days) when added to the period of extension (745 days) is 2,752 days, which is less than fourteen (14) years. Accordingly, the fourteen (14) year limitation set forth in 37 C.F.R. § 1.775(d)(2)-(4) does not operate to further reduce the regulatory review period.

(e) The period of extension (745 days) is less than five (5) years. Accordingly, the five (5) year limitation set forth in 37 C.F.R. § 1.775(d)(5)(i)(ii) does not operate to further reduce the regulatory review period.

$$\begin{aligned}\text{Period of Extension} &= \frac{1}{2} (\text{Adjusted Testing Phase}) + \text{Approval} \\ &\text{Phase} \\ &= \frac{1}{2} (884) + 303 \\ &= \mathbf{745 \text{ days}}\end{aligned}$$

***(13) "A statement that applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to any determination of entitlement to the extension sought."***

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought pursuant to 37 C.F.R. § 1.765.

***(14) "The prescribed fee for receiving and acting upon the application for extension."***

The prescribed fee for receiving and acting upon this application is believed to be \$1,120.00 pursuant to 37 C.F.R. § 1.20(j)(1). The Director is authorized to charge this fee and any additional required fees, or credit any overpayment, to Jones Day Deposit Account No. 50-3013.

***(15) "The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed."***

Please direct all inquiries and correspondence relating to this application to:

Anthony M. Insogna, Esq.  
**JONES DAY**  
222 East 41st Street  
New York, New York 10017  
(212) 326-3939

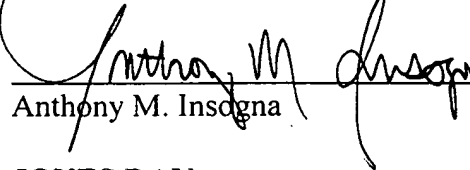
A power of attorney is also enclosed so that the record will reflect correspondence should be addressed to Customer No. 20583.

*(16) "The application under this section must be accompanied by two additional copies of such application (for a total of three copies)."*

This Application is accompanied by two additional copies of such application for a total of three copies as required by 37 C.F.R. § 1.740(b). The undersigned attorney for Applicants hereby states that these copies are accurate and true duplicates of the original.

Date: December 1, 2006

Respectfully submitted,

  
Anthony M. Insogna 35,203  
(Reg. No.)

**JONES DAY**  
222 East 41<sup>st</sup> Street  
New York, NY 10017  
(212) 326-3939

A





US006589508B1

(12) **United States Patent**  
Aberg et al.

(10) Patent No.: **US 6,589,508 B1**  
(45) Date of Patent: **\*Jul. 8, 2003**

(54) **METHODS AND COMPOSITIONS FOR TREATING PULMONARY DISORDERS USING OPTICALLY PURE (R,R) FORMOTEROL**

(75) Inventors: **Gunnar Aberg**, Westborough, MA (US); **John Morley**, Richmond-upon-Thames (GB)

(73) Assignee: **Seppracor Inc.**, Marlborough, MA (US)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(h) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/927,008**

(22) Filed: **Aug. 9, 2001**

#### Related U.S. Application Data

(63) Continuation of application No. 09/535,200, filed on Mar. 27, 2000, which is a continuation of application No. 09/136,109, filed on Aug. 18, 1998, now Pat. No. 6,068,833, which is a continuation of application No. 08/613,382, filed on Mar. 7, 1996, now Pat. No. 5,795,564, which is a continuation-in-part of application No. 08/373,515, filed on Jan. 12, 1995, now abandoned, which is a continuation-in-part of application No. 08/222,319, filed on Apr. 4, 1994, now abandoned, which is a continuation of application No. 07/927,458, filed on Aug. 10, 1992, now abandoned, said application No. 09/136,109, filed on Aug. 18, 1998, is a continuation-in-part of application No. 08/382,744, filed on Feb. 2, 1995, now abandoned, which is a continuation of application No. 08/223,798, filed on Apr. 6, 1994, now abandoned, which is a continuation of application No. 07/862,907, filed on Apr. 3, 1992, now abandoned.

#### (30) Foreign Application Priority Data

Apr. 5, 1991 (GB) ..... 9107196

(51) Int. Cl.<sup>7</sup> ..... A61K 9/00; A61K 9/12; A61K 9/20; A61K 9/70

(52) U.S. Cl. .... 424/45; 424/46; 424/489; 424/400; 424/443; 424/451; 424/464; 514/826

(58) Field of Search ..... 424/45, 46, 400, 424/489, 443, 451, 464; 514/826

#### (56) References Cited

##### U.S. PATENT DOCUMENTS

3,994,974 A	11/1976	Murakami et al.	260/562 A
4,380,534 A	4/1983	Fukui	424/38
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4,917,676 A	4/1990	Heiber	424/449
4,975,466 A	12/1990	Böttcher et al.	514/630
5,795,564 A *	8/1998	Aberg et al.	424/45
6,068,833 A *	5/2000	Aberg et al.	424/45

##### FOREIGN PATENT DOCUMENTS

GB	2255503	11/1992
WO	WO92/05147	4/1992

#### OTHER PUBLICATIONS

Hett et al, Enantio- and Diastereoselective Synthesis of all Four Stereoisomers of Formoterol, Tet. Lett. 38, 1125-1128 (1997).\*

"Comparison of the Action of BD 40 A and some Other  $\beta$ -Adrenoceptor Stimulants of the Isolated Trachea and Atria of the Guinea Pig" H. Ida *Arzneim.-Forsch.* 26,839-842 (1976).

"Cardiorespiratory Activities of 3-Formylamino-4-hydroxy  $\alpha$ -(N-1-methyl-2-methoxyphenethylaminomethyl)-benzylalcohol-bemifumarate (BD 40) and some other  $\beta$ -Adrenoceptor Stimulants in Conscious Guinea Pigs" H. Ida *Arzneim.-Forsch.* 26, 1337-1340 (1976).

"New  $\beta$ -Adrenoreceptor Stimulants. Studies on 3-Acylamino-4-hydroxy- $\alpha$ -(N-substituted aminomethyl)-benzyl Alcohols" Murase et al. *Chem. Pharm. Bull.* 25(6) 1368-1377 (1977).

"Steric Aspects of Agonism and Antagonism at  $\beta$ -Adrenoreceptors: Synthesis of and Pharmacological Experiments With the Enantiomers of Formoterol and Their Diastereomers" Trofast et al. *Chirality* 3443-450 (1991).

"A Three-Month Comparison of Twice Daily Inhaled Formoterol Versus Four Times Daily Inhaled Albuterol in the Management of Stable Asthma <sup>1-3</sup>" Kesten et al. *Am. Rev. Respir. Dis.* 144 622-625 (1991).

"Absolute Configurations of Four Isomers of 3-Formamido-4-hydroxy-..." Murase et al. *Chem. Pharm. Bull.* 26, 1123-29 (1978).

" $\beta$ -Adrenoceptor Ligands: Characterization and Quantification of Drug Effects" Lemoine *Quant. Struct.-Act. Relat.* 11, 211-218 (1992).

"Stereoselectivity in pharmacodynamics and pharmacokinetics" Ariëns *Schweiz. med. Wochenschr.* 120, 131-134 (1990).

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"Racemates Versus Enantiomers in Drug Development: Dogmatism..." Testa et al. *Chirality* 2, 129-133 (1990). Murase et al., "Absolute Configurations of four Isomers of 3-Formamido-4-hydroxy- $\alpha$ -[[N-(p-methoxy- $\alpha$ -methylphenethyl)amino]methyl]benzyl Alcohol, a Potent  $\beta$ -Adrenoreceptor Stimulant," *Chem. Pharm. Bull.* 26:1123-29 (1978).

Testa et al., "Racemates Versus Enantiomers in Drug Development: Dogmatism or Pragmatism?" *Chirality*, 2:129-133 (1990).

\* cited by examiner

Primary Examiner—Michael G. Hartley

Assistant Examiner—M. Haghighatian

(74) Attorney, Agent, or Firm—Heslin Rothenberg Farley & Mesiti, P.C.; Candice J. Clement, Esq.

#### (57) ABSTRACT

A method and composition are disclosed utilizing the pure (R,R) isomer of formoterol, which is a potent bronchodilator with reduced adverse effects, having a low incidence of the development of tolerance and having increased duration of action.

18 Claims, No Drawings

# METHODS AND COMPOSITIONS FOR TREATING PULMONARY DISORDERS USING OPTICALLY PURE (R,R) FORMOTEROL

## CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Ser. No. 09/535,200, filed Mar. 27, 2000 as a continuation of U.S. Ser. No. 09/136,109 (now U.S. Pat. 6,068,833), filed Aug. 18, 1998 as a continuation of U.S. Ser. No. 08/613,382 (now U.S. Pat. No. 5,795,564), filed Mar. 7, 1996 as a continuation-in-part of U.S. Ser. No. 08/373,515 (now abandoned), filed Jan. 12, 1995 as a continuation-in-part of U.S. Ser. No. 08/222,319 (now abandoned), filed Apr. 4, 1994 as a continuation of U.S. Ser. No. 07/927,458 (now abandoned), filed Aug. 10, 1992. U.S. Ser. No. 09/136,109 also claims priority as a continuation-in-part of U.S. Ser. No. 08/382,744 (now abandoned), filed Feb. 2, 1995 as a continuation of U.S. Ser. No. 08/223,798 (now abandoned), filed Apr. 6, 1994 as a continuation of U.S. Ser. No. 07/862,907 (now abandoned), filed Apr. 3, 1992 claiming priority of Great Britain application 9107196.9, filed Apr. 5, 1991. The entire disclosures of each of the prior applications are incorporated herein by reference.

## BACKGROUND OF THE INVENTION

This invention relates to novel compositions of matter containing optically pure (R,R) formoterol. These compositions possess potent, long-lasting bronchodilating activity as  $\beta$ -adrenergic agonists while avoiding or reducing adverse effects including but not limited to muscle tremor and tachycardia as well as avoiding or reducing the development of tolerance or hypersensitivity on repeated administration. The compositions also provide an improved duration of action. This invention also relates to methods of treating asthma, bronchitis, emphysema, bronchospasms, and other ailments in patients with obstructive airway or allergic disorders while avoiding adverse effects, development of tolerance or hypersensitivity on repeated administration or a limited pattern of bronchial distribution when administered by inhalation.

The active compound of these compositions and methods is an optical isomer of formoterol, which is described by Ida in *Arzneim. Forsch.* 26, 839-842 and 1337-1340 (1976) and in U.S. Pat. No. 3,994,974. Chemically, the active compound is N-hydroxy-5-(1-hydroxy-2-[(2-(4-methoxyphenyl)methylethyl)amino]ethyl)phenylformamide, which exists as two enantiomeric pairs of diastereomers. Of these, the R,R diastereomer is the most active and, when substantially optically pure, will be hereinafter referred to as (R,R) formoterol. Formoterol is available commercially only as a racemic diastereomer, (R,R) plus (S,S) in a 1:1 ratio, and the generic name formoterol refers to this enantiomeric mixture. The racemic mixture of ( $\pm$ ) formoterol that is commercially available for administration is a dihydrate of the fumarate salt.

When two chiral centers occur in the same molecule each of them can exist in two possible configurations. This gives rise to four combinations: (R,R), (S,S), (R,S) and (S,R). (R,R) and (S,S) are mirror images of each other and are therefore enantiomers which share chemical properties and melting points just like any other enantiomeric pair. (R,S) and (S,R) are similarly an enantiomeric pair. The mirror images of (R,R) and (S,S) are not, however, superimposable on (R,S) and (S,R). This relationship is called

diastereomeric, and (R,R) is a diastereomer of (R,S). Formoterol, having two chiral centers, falls into this category.

Adrenergic or sympathomimetic drugs are so called because they are understood to exert their effect through their action on the body's adrenergic receptors of which there are three functionally divided types, the  $\alpha$ ,  $\beta_1$  and  $\beta_2$  receptors. On the basis of their interaction with these three receptor types, the adrenergic or sympathomimetic drugs are in turn classifiable into three groups:

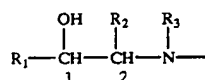
- 1.1 Non-selective sympathomimetic drugs;
- 1.2 Non-selective  $\beta$  sympathomimetic drugs; and
- 1.3 Selective  $\beta_2$  sympathomimetic bronchodilator drugs.

Drugs of group 1.1 exert both  $\alpha$  and  $\beta$  sympathomimetic effects. They include the drug substances adrenaline and ephedrine. Both adrenaline and ephedrine are known clinically as bronchodilators. Though adrenaline, despite side effect induced via its  $\alpha$ -sympathomimetic properties, is still used by some practitioners for the treatment of acute asthma, both adrenaline and ephedrine have been largely superseded in asthma therapy.

The drugs of group 1.2 have both  $\beta_1$  and  $\beta_2$  sympathomimetic activity but no, or only limited,  $\alpha$ -sympathomimetic activity. Of the group 1.2 drugs, isoprenaline is the best known representative. Isoprenaline differs from the drugs of group 1.3 in its faster onset but shorter duration of action and its cardiac stimulating effects which result largely from its  $\beta_1$  activity. Though isoprenaline has previously been extensively used as bronchodilator therapy in asthma, its use has today become clinically restricted. Thus, in the UK, a rise in the rate of asthma death in the 1960's believed to have been specifically associated with isoprenaline usage has resulted in discontinuation of its clinical application.

The selective  $\beta_2$  sympathomimetic bronchodilator drugs of group 1.3 (herein referred to for convenience collectively as "Group 1.3 drugs") act, as their name implies, selectively on the  $\beta_2$  adrenergic receptors. The Group 1.3 drugs include for example, the drug substances terbutaline, albuterol, fenoterol, isoetharine, metaproterenol and, more recently, the so-called "long acting selective  $\beta_2$  sympathomimetic bronchodilator drug substances" formoterol, bambuterol and salmeterol. All of the above recited Group 1.3 drugs are commercially available and clinically used, generally in pharmaceutically acceptable salt form, e.g. as the sulphate, hydrobromide, hydrochloride, fumarate or methane-sulfonate or, where appropriate, one or other of the hydrate forms thereof.

Group 1.3 drugs characteristically contain as part of their structure an ethanolamine or 2-amino-ethanol moiety of formula I



(I)

in which  $\text{R}_1$  is an aromatic group. Commonly  $\text{R}_1$  is 3,4- or 3,5-dihydroxyphenyl or 4-hydroxy-3-hydroxymethylphenyl.  $\text{R}_1$  may also be 3-formylamino-4-hydroxyphenyl, as in the case of formoterol.  $\text{R}_2$  and  $\text{R}_3$  in formula I are commonly H. Since the formula I moiety comprises at least 1 asymmetric carbon atom (C1 in formula I), all of the Group 1.3 drugs exist in optically active isomeric form, with the chiral carbon atom having the (R) or (S) configuration [as designated using the Cahn-Ingold-

Prelog system (Angew. Chem. Intern. Ed. 5, 385-415 (1966)). When the Cl carbon atom is the sole asymmetric carbon atom present, Group 1.3 drugs thus exist as individual (R) or (S) enantiomers or in racemic [(RS)] form, i.e. as a 50:50 mixture of the (R) and (S) enantiomers.

Individual Group 1.3 drugs in which R<sub>2</sub> in the formula I moiety is other than H, or in which the remainder of the molecule includes an asymmetric carbon atom (e.g. formoterol) exist in a variety of isomeric forms, i.e. in individual (R,R), (S,S) (R,S) and (S,R) isomeric form, as racemic [(RS,RS) and (RS,SR)] mixtures comprising the (R,R) plus (S,S) and (R,S) plus (S,R) enantiomeric pairs, as well as in the form of diastereomeric mixtures comprising all four isomeric forms.

The Group 1.3 drugs can be administered orally, parenterally or (most commonly) by inhalation, e.g. using nebulizers or metered aerosol devices or as inhaled powders. Inhalation of Group 1.3 drugs presently represents the mainstay of bronchodilator therapy for the treatment of asthma of all grades of severity. The duration of bronchodilatation induced by the majority of Group 1.3 drugs is relatively short and they are employed to relieve asthma attack as and when it occurs. As indicated above, the more recently introduced Group 1.3 drugs, such as formoterol, are characterized by their longer duration of action and hence apparent reduced frequency of dosaging required.

Although the Group 1.3 drugs are effective and generally seem to be well tolerated, their safety, especially at high dosages, has been questioned over many years and numerous reports have appeared on the adverse effects of Group 1.3 drug therapy (see e.g. Paterson et al: *American Review of Respiratory Disease* 120, 844-1187 (1979) especially at page 1165 et seq.). More recently, from New Zealand, where a continuing increase in asthma death has been recorded, two case control studies reported in *The Lancet* have linked increase in asthma mortality to use of the Group 1.3 drug, fenoterol—see in particular: Editorial “ $\beta_2$  agonists in asthma: relief, prevention, morbidity”, *Lancet* 336, 1411-1412 (1990). A subsequently reported Canadian study finds that the use of inhaled Group 1.3 drugs, principally fenoterol and albuterol, is associated with “an increased risk of the combined outcome of fatal and near-fatal asthma, as well as of death from asthma alone”—see Spitzer et al., *New England J. Med.* 326 (8), 501-506 (1992) and the Editorial to the same issue at page 560.

Various possible explanations for observed episodes of increased airway obstruction, arterial hypoxaemia or “anomalous” or “paradoxical” bronchospasm, as well as increased morbidity associated with Group 1.3 drug usage, in particular long term/high dose usage, have been proposed. These have included, for example, reactive myogenic tone, increased inflammatory burden, adrenoceptor tachyphylaxis and induction of airway hyperreactivity, as well as the involvement of spasmogenic drug metabolic products or long term influence of aerosol spray propellants—see e.g. Paterson et al. loc. cit. and Morley et al., *Eur. Respir. J.* 3, 1-5 (1990).

There is mounting concern within the medical profession as to the potential dangers of Group 1.3 drug usage in asthma therapy. To quote the *Lancet* editorial already referred to:

“These studies raise serious question about the use of  $\beta$  agonists [i.e. Group 1.3 drugs]. The findings of Sears et al. could be interpreted as supporting the current trend towards earlier use of corticosteroids and other preventers of inflammation [for asthma therapy] rather than perseverance with an escalating bronchodilator regimen. The findings of the Nottingham and Dunedin

groups also indicate that there is some way to go before long acting  $\beta_2$  agonist preparations such as salmeterol and formoterol can be unreservedly recommended for routine use in the management of asthma. There seem to be clear advantages of compliance and possibly of anti-inflammatory activity associated with such agents, but the potential for adverse effects cannot be ignored. Clinicians researchers and pharmaceutical companies must now attempt to redefine the use of  $\beta_2$  agonists in asthma.” [Emphasis added.]

Equally there has been evident inability or reluctance to conceive of any problem in relation to Group 1.3 drug therapy as being inherent in Group 1.3 drugs themselves or as hitherto employed—cf. the following, taken from the editorial in the *New England Journal of Medicine* also previously referred to:

“Although . . . too much reliance is placed on beta-agonists (Group 1.3 drugs), it is difficult to believe that the problem is related directly to the more regular use of inhaled beta-agonists.”

While the suitability, in particular of high-dose or long-term, Group 1.3 drug therapy has long been a subject of debate and, more recently, acute question, the practice of administering drugs of this group as racemic mixtures has continued. This practice has been accepted by drug registration authorities world-wide and even the most recently introduced of the Group 1.3 drugs have been developed for clinical use as racemic mixtures. This practice is based upon the assumption or understanding that the non-bronchodilator component of the racemic mixture, i.e. the bronchodilatorily less or inactive enantiomer (distomer) is devoid of any relevant drug effect and can thus be administered together with the bronchodilatorily active isomer (eutomer) essentially as inactive ballast and without risk to the patient. The teaching of the present invention thus stands in stark opposition to long, widely established and continuing practice. The present invention thus runs contrary to the wisdom of the art. In that the Group 1.3 drugs clearly offer very considerable potential benefit for bronchodilator usage in asthma, the need to find a means of avoiding, ameliorating or restricting disadvantages inherent in their use is urgent and crucial. By meeting this need, the present invention may be anticipated to bring immeasurable benefit both to the medical profession and the world asthma population.

Formoterol, which is the subject of the present invention, is available only as a racemic mixture of the (R,R) and (S,S) diastereomers. Trofast et al. [*Chirality* 3, 443-450 (1991)] have described the preparation of each of the substantially pure isomers. They concluded that “Since the (S,S)-enantiomer is practically inactive there is from this point of view no reason for its removal from the racemate in pharmaceutical preparations . . .”.

Formoterol's primary use is as a long-acting bronchodilator for the relief of reversible bronchospasm in patients with obstructive airway disease such as asthma, bronchitis and emphysema.

Asthma, bronchitis and emphysema are known as Chronic Obstructive Pulmonary Diseases (COPD). COPD is characterized as generalized airways obstruction, particularly of small airways, associated with varying degrees of symptoms of chronic bronchitis, asthma, and emphysema. The term COPD was introduced because these conditions often coexist, and it may be difficult in an individual case to decide which is the major condition producing the obstruction. Airways obstruction is defined as an increased resistance to airflow during forced expiration. It may result from narrowing or obliteration of airways secondary to intrinsic airways

disease, from excessive collapse of airways during a forced expiration secondary to pulmonary emphysema, from bronchospasm as in asthma, or may be due to a combination of these factors. Although obstruction of large airways may occur in all these disorders, particularly in asthma, patients with severe COPD characteristically have major abnormalities in their small airways, namely those less than 2 mm internal diameter, and much of their airways obstruction is situated in this zone. The airways obstruction is irreversible except for that which can be ascribed to asthma.

Asthma is a reversible obstructive lung disorder characterized by increased responsiveness of the airways. Asthma can occur secondarily to a variety of stimuli. The underlying mechanisms are unknown, but inherited or acquired imbalance of adrenergic and cholinergic control of airways diameter has been implicated. Persons manifesting such imbalance have hyperactive bronchi and, even without symptoms, bronchoconstriction may be present. Overt asthma attacks may occur when such persons are subjected to various stresses, such as viral respiratory infection, exercise, emotional upset, nonspecific factors (e.g., changes in barometric pressure or temperature), inhalation of cold air or irritants (e.g., gasoline fumes, fresh paint and noxious odors, or cigarette smoke), exposure to specific allergens, and ingestion of aspirin or sulfites in sensitive individuals. Psychologic factors may aggravate an asthmatic attack but are not assigned a primary etiologic role.

Persons whose asthma is precipitated by allergens (most commonly airborne pollens and molds, house dust, animal danders) and whose symptoms are IgE-mediated are said to have allergic or "extrinsic" asthma. They account for about 10 to 20% of adult asthmatics; in another 30 to 50%, symptomatic episodes seem to be triggered by non-allergenic factors (e.g., infection, irritants, emotional factors), and these patients are said to have nonallergic or "intrinsic" asthma. In many persons, both allergenic and nonallergenic factors are significant. Allergy is said to be a more important factor in children than in adults, but the evidence is inconclusive.

Chronic bronchitis (unqualified) is a condition associated with prolonged exposure to nonspecified bronchial irritants and accompanied by mucus hypersecretion and certain structural changes in the bronchi. Usually associated with cigarette smoking, it is characterized clinically by chronic productive cough. The term chronic obstructive bronchitis is used when chronic bronchitis is associated with extensive abnormalities of the small airways leading to clinically significant airways obstruction. (Pulmonary emphysema is enlargement of the air spaces distal to terminal nonrespiratory bronchioles, accompanied by destructive changes of the alveolar walls.) The term chronic obstructive emphysema is used when airways obstruction is also present and where it is clear that the major features of the disease can be explained by emphysematous changes in the lungs.

Many of the  $\beta_2$  agonists cause somewhat similar adverse effects. These adverse effects include but are not limited to the central nervous system symptoms such as hand tremors, muscle tremors, nervousness, dizziness, headache and drowsiness; respiratory side effects such as dyspnea, wheezing, drying or irritation of the oropharynx, coughing, chest pain and chest discomfort; cardiovascular effects such as palpitations, increased heart rate, and tachycardia. According to Trofast et al. (op. cit.) (R,R) formoterol is primarily a chronotropic agent in vitro with inotropic effects showing up at higher concentrations. The chronotropic effects are reported at concentrations that are higher than those at which relaxation of tracheal muscle

(bronchodilation) is seen.  $\beta$ -Agonists (e.g. dobutamine) are known in general to exhibit inotropic activity. In addition, racemic  $\beta_2$ -agonists can cause angina, vertigo, central stimulation and insomnia, airway hyperreactivity (hypersensitivity), nausea, diarrhea, dry mouth and vomiting. As with other pharmaceuticals  $\beta_2$ -agonists sometimes cause systemic adverse effects such as weakness, fatigue, flushed feeling, sweating, unusual taste, hoarseness, muscle cramps and backaches.

Furthermore, patients have a tendency to develop a tolerance to the bronchodilating effect of the racemic mixture of formoterol. This is related to desensitization, which is one of the most clinically significant phenomena involving the beta-adrenergic receptor. It has been observed that patients in prolonged beta-agonist therapy have a tendency to increase the dosage of drug they use. This occurs because after prolonged administration, the beta-receptor appears to become desensitized to the agonist, thus requiring larger doses of the compound to effect an equivalent physiological response.

The problem of desensitization is especially significant in the treatment of diseases involving bronchospasms, such as asthma. The treatment of asthma usually involves the self-administration either orally or by aerosol, of beta-adrenergic agonists such as the racemic (R,R) (S,S) mixture of formoterol. These agonists mediate bronchodilation and promote easier breathing. Asthmatic patients utilizing  $\beta$ -agonists for a prolonged time gradually increase the self-administered dose in order to get a sufficient amount of bronchodilation and relief in breathing. As a result of this increased dosage, the agonist concentration builds to a sufficient level so as to enter the peripheral circulation where it acts on the beta receptors of the heart and vasculature to cause cardiovascular stress and other adverse effects.

Moreover, when administering the racemic mixture of formoterol by inhalation, because of particle size and air flow distribution characteristics of the racemic mixture of formoterol, the distribution of the compound into the smaller bronchioles is limited, which results in a decreased effectiveness of the compound.

It is therefore desirable to find a compound with the therapeutic characteristics of formoterol which would not have the above described disadvantages.

#### SUMMARY OF THE INVENTION

It has now been discovered that the (R,R) isomer of formoterol is an effective bronchodilator that does not have certain adverse effects associated with the administration of the racemic mixture of (R,R) and (S,S) formoterol. The present invention includes administering to a human (R,R) formoterol to cause bronchodilation and to decrease said adverse effects. Furthermore, it has also been discovered that by administering only the (R,R) isomer of formoterol there is decreased tolerance and hypersensitivity to the compound, relative to that seen when the racemic mixture of formoterol is administered. In addition, it has been discovered that by administering the (R,R) isomer of formoterol by inhalation, it is possible to obtain improved distribution of the compound in the smaller bronchioles which results in an increased bronchodilating effect. In addition, an increased duration of the beneficial effects is observed upon administration of the substantially pure (R,R) enantiomer, as compared to administration of the racemic drug.

The present invention also includes novel compositions of matter containing optically pure (R,R) formoterol which is useful as a bronchodilator. These novel compositions also avoid the above described adverse effects, increased toler-

ance or limited pattern of distribution when administered by inhalation, associated with the racemic mixture of formoterol.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses a method of eliciting a bronchodilator effect while avoiding the concomitant liability of adverse effects, development of tolerance, or limited pattern of bronchial distribution when administered by inhalation, which comprises administering to a human in need of bronchodilation an amount sufficient to alleviate bronchospasms, but insufficient to cause said adverse effects, development of tolerance, hypersensitivity or limited pattern of bronchial distribution when administered by inhalation, of (R,R) formoterol or a pharmaceutically acceptable salt thereof, substantially free of its (S,S) stereoisomer. The bronchodilator effects are achieved by utilizing the highly potent  $\beta$ -adrenergic effects of the (R,R) isomer of formoterol while substantially limiting the adverse effects, development of tolerance, hypersensitivity or limited pattern of bronchial distribution when administered by inhalation, by decreasing or eliminating the amount of (S,S) isomer in the composition.

As hereinbefore described in relation to formula I, Cl in the enantiomer of Group 1.3 drugs characteristically has the (R) configuration. In the case of Group 1.3 drugs having two asymmetric carbon atoms, the enantiomer could thus be the (R,R) or (R,S) isomer. Although we have found that it is the (R,R) enantiomer which has the greatest bronchodilator potency, Group 1.3 drugs having two asymmetric carbon atoms have hitherto been used in the clinic generally in the form of the (RS,RS) racemic mixture.

The present invention also encompasses a bronchodilator composition for the treatment of a patient in need of bronchodilating therapy which comprises an amount sufficient to alleviate bronchospasms but insufficient to cause adverse effects, development of tolerance or limited bronchial distribution when administered by inhalation, of (R,R) formoterol or a pharmaceutically acceptable salt thereof, substantially free of its (S,S) stereoisomer.

The racemic mixture of formoterol causes bronchial smooth muscle relaxation and modulates inhibition of mediator release effect; however, this racemic mixture causes adverse effects, leads to the development of tolerance and the development of hypersensitivity and results in a limited pattern of bronchial distribution when administered by inhalation. Utilizing the (R,R) isomer of formoterol results in diminished adverse effects, decreased development of tolerance and increased bronchial distribution when the compound is administered by inhalation. Thus, it is much more desirable to use the (R,R) isomer of formoterol when treating asthma, bronchitis, emphysema or to alleviate bronchospasms.

Furthermore, although there is some variability from one patient to another, it is generally observed that, by administering an effective amount of only the (R,R) isomer of formoterol it is possible to accomplish a more "targeted" therapy. A more "targeted" therapy means that by using the (R,R) isomer the compound's activity can be taken advantage of without also having consequences of the pharmacologic effects of the (S,S) isomer which are observed upon administration of the racemic mixture. This is important since it is not desirable for all patients to be administered a compound with such a multifaceted spectrum of activity.

The present invention provides a method or use for the treatment of inflammatory airways disease, in particular for

effecting bronchodilation, e.g. as a means of alleviating airways obstruction, in particular acute airways obstruction, e.g. asthma attack, occurring in such disease. The invention thus provides symptomatic, rather than prophylactic, therapy for such disease. The teaching of the present invention is applicable in the therapy of inflammatory or obstructive airways disease, in particular any such disease for which Group 1.3 drug therapy is commonly practiced, for example chronic obstructive pulmonary disease, e.g. consequential to cystic fibrosis, emphysema and, especially, chronic bronchitis and, most especially, asthma.

The present invention avoids deleterious side effects hereinbefore resulting or observed in, e.g. asthmatic, patients consequent to conventional clinical usage of Group 1.3 drugs as racemic mixtures. In particular the invention provides means to avoid, ameliorate or restrict deleterious side effects, e.g. side effects deleterious to the airways. Thus the invention provides means to avoid, ameliorate or restrict exacerbation of disease status, for example basal disease, e.g. basal asthmatic, status or to avoid, ameliorate or restrict compromise or deterioration of lung function, or any other side effect concomitant to conventional clinical usage, for example "anomalous", "rebound" or "paradoxical" bronchospasm and, especially, increase in airway obstruction, exacerbation of late asthmatic response or non-specific bronchial reactivity or arterial hypoxemia. Without limiting the present invention to any specific theory or mode of action, the present invention is in particular to be understood as providing a means for the avoidance, amelioration or restriction of exacerbation of airways hyperreactivity and/or of an inflammatory or other event associated with, or which is an etiological component of, inflammatory or obstructive airways disease, e.g. asthma. Such events are to be understood as including for example, inflammatory cell infiltration of the lungs or airways, connective tissue deposition or smooth muscle hyperplasia within the lungs or airways or other morphological change associated with asthmatic status. The present invention also provides a means of preventing or reducing morbidity, e.g. asthma morbidity, ascribable to conventional, e.g. high dosage or long term, Group 1.3 drug usage.

The present invention is especially applicable in the therapy of bronchial asthma of whatever type or genesis. It is applicable to both intrinsic and extrinsic asthma. It is especially applicable to the treatment of allergic or atopic (i.e. IgE-mediated) asthma or non-atopic asthma, as well as exercise induced asthma, occupational asthma, asthma induced following bacterial infection or drug, e.g. aspirin, ingestion and other non-allergic asthmas. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting chronic cough or wheezing symptoms, in particular at night, and diagnosed or diagnosable as "wheezy infants", i.e. as embracing the treatment of "wheezy infant syndrome". Other diseases to which the present invention is in particular applicable include for example chronic obstructive pulmonary or airways disease (COPD or COAD).

The term "adverse effects" includes but is not limited to hand tremors, muscle tremors, nervousness, palpitations, tachycardia, increased heart rate, dyspnea, coughing, chest pain, chest discomfort, drying or irritation of the oropharynx and wheezing. Also included in the term "adverse effects" are headaches, dizziness, fatigue, hoarseness, backaches, nausea, vomiting, drowsiness, weakness, flushed feeling, sweating, unusual taste, muscle cramps, weakness, angina, vertigo, central stimulation, hypersensitivity and insomnia.

The term "substantially free of the (S,S) stereoisomer" as used herein means that the composition contains at least

about 90% by weight of (R,R) formoterol and 10% or less by weight of (S,S) formoterol. In a more preferred embodiment the composition contains at least 99% by weight (R,R) formoterol and 1% or less of (S,S) formoterol. In the most preferred embodiment the composition contains greater than 99% by weight of (R,R) formoterol and less than 1% by weight of (S,S) formoterol.

The term "eliciting a bronchodilator effect" means relief from the symptoms associated with obstructive airway diseases, which include but are not limited to respiratory distress, wheezing, coughing, shortness of breath, tightness or pressure in the chest and the like.

The term "development of tolerance" means that when administering the racemic mixture of formoterol in repeated dosage or over a period of time, the amount of the compound given to the patient must be increased in order to achieve the same effect as the lower dosage given at an earlier time.

The term "limited pattern of bronchial distribution when administered by inhalation" means that therapeutically effective quantities cannot penetrate into smaller bronchioles.

The mixture of formoterol isomers can be prepared according to U.S. Pat. No. 3,994,974. The diastereomers may be separated as described by Murase et al. [*Chem. Pharm. Bull.* 25, 1368-13 (1977)]. The individual isomers of formoterol may be obtained as described by Trofast et al. (op. cit.) by stereocontrolled synthesis from optically active starting material or by resolution of a mixture of enantiomers (i.e., the racemic mixture) using conventional means, such as an optically active resolving acid. Other standard methods of resolution known to those skilled in the art including but not limited to simple crystallization and chromatographic resolution can be used. (See for example, *Stereochemistry of Carbon Compounds*, E. L. Eliel, McGraw Hill 1962; "Tables of Resolving Agents," S. A. Wilen and Lochmuller, L. H. et al., 1975, *J. Chromatogr.* 113(3): 283-302.) Additionally, the optically pure (R,R) isomer can be prepared from the racemic mixture by enzymatic biocatalytic resolution. See, for example, U.S. Pat. Nos. 5,057,427 and 5,077,217, the disclosures of which are incorporated herein by reference.

The magnitude of a prophylactic or therapeutic dose of (R,R) formoterol in the acute or chronic management of disease will vary with the severity of the condition to be treated, and the route of administration. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose ranges when administered by inhalation, for the conditions described herein, is from about 1  $\mu$ g to about 100  $\mu$ g, in single or divided doses. Preferably, a daily dose range should be between about 6  $\mu$ g to about 25  $\mu$ g, in single or divided doses, while most preferably, a daily dose range should be between about 12  $\mu$ g to about 25  $\mu$ g, in from two to four divided doses. In managing the patient, the therapy should be initiated at a lower dose, perhaps about 3  $\mu$ g to about 12  $\mu$ g, and increased up to about 2x12  $\mu$ g or higher depending on the patient's global response. When administered orally, preferably as a tablet, the preferred dose range is from 0.1 to 1.0 mg per day. It is further recommended that children, and patients over 65 years, and those with impaired renal, or hepatic function, initially receive low doses, and that they be titrated based on individual responses) and blood level(s). It may be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician would know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response.

The terms "an amount sufficient to alleviate bronchospasms but insufficient to cause said adverse effects" are encompassed by the above-described dosage amounts and dose frequency schedule.

Any suitable route of administration may be employed for providing the patient with an effective dosage of (R,R) formoterol. For example, oral, rectal, parenteral (subcutaneous, intramuscular, intravenous), transdermal, and like forms of administration may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, patches, and the like.

The pharmaceutical compositions of the present invention comprise (R,R) formoterol as the active ingredient, or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic ingredients.

The term "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable non-toxic acids including inorganic acids and organic acids. Suitable pharmaceutically acceptable acid addition salts for the compound of the present invention include acetic, benzenesulfonic (besylate), benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, and the like. The fumaric acid salt is particularly preferred.

The compositions of the present invention include compositions such as suspensions, solutions and elixirs; aerosols; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like. The compositions include compositions suitable for oral, rectal, parenteral (including subcutaneous, transdermal, intramuscular, and intravenous) and inhalation, although the most suitable route in any given case will depend on the condition being treated and the nature and severity of that condition. The most preferred routes of the present invention are: (1) oral by either tablets or capsules, (2) inhalation and (3) transdermal by patch. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In addition to the common dosage forms set out above, the compounds of the present invention may also be administered by controlled release means and/or delivery devices such as those described in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, the disclosures of which are hereby incorporated by reference.

The invention is further defined by reference to the following examples describing in detail the pharmacological characterization of the compound, and the preparation of compositions of the present invention. It will be apparent to those skilled in the art, that many modifications, both to materials, and methods, may be practiced without departing from the purpose and interest of this invention.

## EXAMPLES

### Procedure 1

$\beta$ -Adrenergic Receptor Phosphorylation by  $\beta$ -Adrenoreceptor Kinase. Reconstituted  $\beta$ -adrenergic receptor is incubated with  $\beta$ -adrenoreceptor kinase in a buffer containing 20 mM Tris-HCl, pH 7.5, 2 mM EDTA, 20 mM NaCl, 6 mM  $MgCl_2$ , 6 mM sodium phosphate, 0.5 mM ascorbic acid 60  $\mu$ M [ $\gamma$ - $^{32}P$ ]ATP at 30° C. The incubations

also contain varying concentrations of one of the following: buffer (control), (-)-isoproterenol, R,R-formoterol, S,S-formoterol or racemic formoterol. The incubations are stopped by the addition of SDS sample buffer followed by electrophoresis on 10% homogeneous polyacrylamide gels. Stoichiometries of phosphorylation are determined by cutting and counting the dried gel as described in Benovic J. L. et al. [*J. Biol. Chem.* 9026-9032 (1987)].

#### Procedure 2

Purification of component proteins. The  $\beta$ -adrenergic receptor from hamster lung is purified to >95% homogeneity by sequential affinity chromatography and high performance liquid chromatography as described by Benovic et al. [*Biochemistry* 23, 4510-4518 (1984)]. The stimulatory guanine nucleotide regulatory protein is purified from membranes derived from bovine cerebral cortex. The membranes, solubilized with 1% cholate, are centrifuged and the resulting supernatant chromatographed on DEAE-Sephacel, Ultrogel AcA34, octyl-Sepharose, and hydroxyapatite, with a final step on DEAE-Sephacel, as adapted from Strittmatter and Neer [*Proc. Natl. Acad. Sci.* 77, 6344-6348 (1980)]. The resulting protein should be 50-90% pure by Coomassie Blue staining of polyacrylamide gels. The catalytic moiety of adenylate cyclase is solubilized from bovine caudate with sodium cholate and isolated from the other components of the system by Sepharose 6B chromatography as described in Strittmatter and Neer (op. cit.).  $\beta$ -Adrenoreceptor kinase is purified from bovine cerebral cortex. The tissue is homogenized, and the resulting high speed supernatant fraction is precipitated with 13-26% ammonium sulfate. This material is then chromatographed on Ultrogel AcA34, DEAE-Sephacel, and CM-Fractogel. The preparations used should be 10-20% pure as judged by Coomassie Blue staining of SDS-polyacrylamide gels.

Assay for adenylate cyclase activity. The co-reconstitution of the purified proteins is carried out as described in Cerione et al. [*J. Biol. Chem.* 259, 9979-9982 (1984)]. The pelleted proteins are incubated for 15 min. at 37° C. in 30 mM Tris-HCl, pH 7.5 containing 1 mM ATP, 2  $\mu$ Ci of [ $\alpha$ -<sup>32</sup>P]ATP 0.14 mM cAMP, 100 mM sucrose, 0.4 mM dithiothreitol, 2.8 mM phosphoenol pyruvate, 5.2  $\mu$ g/mL pyruvate kinase, 10  $\mu$ g/mL of myokinase, 5 mM MgCl<sub>2</sub>, and varying concentrations of racemic formoterol, (R,R) formoterol and (S,S) formoterol (total volume=0.5 mL). The reaction is stopped by the addition of 0.25 mL 2% sodium dodecylsulfate containing 40 mM ATP and 1.4 mM cAMP at pH 7.5. Water (0.5 mL) is added to each reaction tube and the contents placed on a Dowex 50AG WX4 resin. The eluate from the columns plus two successive water washes (1.0 mL) are discarded. The columns are then eluted with 3 mL water and the eluates collected in test tubes. Each fraction is diluted with 0.2 mL of 1.5 M imidazole HCl, pH 7.2. The tubes from each concentration (run in triplicate) are combined and decanted into columns containing 0.6 g neutral alumina that has been previously washed with 0.1 M imidazole HCl, pH 7.5. The eluate is collected in scintillation vials containing 12 mL Aquasol®. After the columns are completely drained, they are washed with an additional 1 mL of 0.1 M imidazole HCl, pH 7.5 which is collected in the same scintillation vials. The concentration of <sup>32</sup>P-cAMP is determined in each sample.

The metabolic rates of the racemate and the isomers of formoterol have been studied in human liver tissues. It was unexpectedly found that the metabolic rate is significantly slower for (R,R) formoterol than for the racemate and for the SS-isomer. These new findings show that the clearance

( $V_{max}/K_m$ ) was 152 for (R,R) formoterol, 381 for (S,S) formoterol and 489 for (R,R/S,S) formoterol. It is possible to calculate the relative biological half-lives ( $t_{1/2}$ ) of the RR-isomer and the racemate from these data, using the formula  $Cl = Vd \times 0.693/t_{1/2}$ . Assuming the same distribution volume [ $Vd=1$ ] for all three compounds, the relative half-lives are 4.6 for (R,R) formoterol and 1.4 for (R,R/S,S) formoterol. Thus, the half-life of (R,R) formoterol is approximately three times longer than the half-life of the racemate. This demonstrates a significant advantage of the pure RR enantiomer in terms of its duration of action as well as diminution of side effects.

#### Example 1

ORAL FORMULATION		
Tablets:		
Formula	Quantity per Tablet (mg.)	
	A	B
(R,R) formoterol	0.12	0.25
Lactose	41.38	41.25
Cornstarch	3.0	3.0
Water (per thousand Tablets)*	30.0 ml	30.0 ml
Cornstarch	5.00	5.00
Magnesium Stearate	0.50	0.50
	50.00	50.00

\*The water evaporates during manufacture

The formoterol is blended with the lactose until a uniform blend is formed. The smaller quantity of cornstarch is blended with the water to form the resulting cornstarch paste. This is then mixed with said uniform blend until a uniform wet mass is formed. The remaining cornstarch is added to the resulting wet mass and mixed until uniform granules are obtained. The granules are then screened through a suitable milling machine, using a 1/4 inch stainless steel screen. The milled granules are then dried in a suitable drying oven until the desired moisture content is obtained. The dried granules are then milled through a suitable milling machine, using 1/4 mesh stainless steel screen. The magnesium stearate is then blended and the resulting mixture is compressed into tablets of desired shape, thickness, hardness and disintegration.

#### Example 2

ORAL INHALATION	
Formula	Quantity contained in Each Metered Dose Dispenser 7.5 mL (10.5 g) Canister
(R,R) formoterol	1.8 mg
trichloromonofluoromethane	5.16 g
dichlorodifluoromethane	5.16 g
sorbilan trioleate	0.105 g

The metered dose dispenser contains micronized (R,R) formoterol fumarate dihydrate in suspension. Each actuation delivers 6  $\mu$ g of (R,R) formoterol fumarate dihydrate from the mouthpiece. Each canister provides about 300 inhalations.

What is claimed is:

1. A method of treating asthma in human, the method comprising administering to the human a therapeutically effective amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof.

2. The method according to claim 1, wherein the amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof, is administered orally, transdermally, by inhalation, by subcutaneous injection or by intravenous infusion.

3. The method according to claim 2, wherein the amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof, is administered by inhalation at a dosage of about 1  $\mu$ g to about 100  $\mu$ g per day.

4. The method according to claim 3, wherein the amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof, is administered is about 6  $\mu$ g to about 25  $\mu$ g per day.

5. The method according to claim 3, wherein the formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, comprises formoterol fumarate dihydrate.

6. The method according to claim 5, wherein the formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, comprises formoterol fumarate dihydrate.

7. A method of treating or preventing bronchospasm in a human, the method comprising administering to the human a therapeutically effective amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof.

8. The method according to claim 7, wherein the amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof, is administered orally, transdermally, by inhalation, by subcutaneous injection or by intravenous infusion.

9. The method according to claim 8, wherein the amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof, is administered by inhalation at a dosage of about 1  $\mu$ g to about 100  $\mu$ g per day.

10. The method according to claim 9, wherein the amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof, is administered is about 6  $\mu$ g to about 25  $\mu$ g per day.

11. The method according to claim 9, wherein the formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, comprises formoterol fumarate dihydrate.

12. The method according to claim 11, wherein the formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, comprises formoterol fumarate dihydrate.

13. A method of eliciting bronchodilation effect in a human, the method comprising administering to the human a therapeutically effective amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof.

14. The method according to claim 13, wherein the amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof, is administered orally, transdermally, by inhalation, by subcutaneous injection or by intravenous infusion.

15. The method according to claim 14, wherein the amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof, is administered by inhalation at a dosage of about 1  $\mu$ g to about 100  $\mu$ g per day.

16. The method according to claim 15, wherein the amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof, is administered is about 6  $\mu$ g to about 25  $\mu$ g per day.

17. The method according to claim 15, wherein the formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, comprises formoterol fumarate dihydrate.

18. The method according to claim 17, wherein the formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, comprises formoterol fumarate dihydrate.

\* \* \* \* \*



B



## Patent Assignment Abstract of Title

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For pending or abandoned applications please consult USPTO staff.**

**Total Assignments: 1**

**Patent #:** 5795564    **Issue Dt:** 08/18/1998    **Application #:** 08613382    **Filing Dt:** 03/07/1996

**Inventors:** GUNNAR ABERG, JOHN MORLEY

**Title:** METHODS AND COMPOSITIONS FOR TREATING PULMONARY DISORDERS USING OPTICALLY  
PURE (R,R)-FORMOTEROL

**Assignment: 1**

**Reel/Frame:** 008018 / 0813

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**Pages:** 4

**Conveyance:** ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

**Assignors:** ABERG, GUNNAR  
MORLEY, JOHN

**Exec Dt:** 06/20/1996

**Exec Dt:** 06/24/1996

**Assignee:** SEPRACOR, INC.  
33 LOCKE DRIVE  
MARLBOROUGH, MASSACHUSETTS 01752

**Correspondent:** HESLIN & ROTHENBERG, P.C.  
PHILIP E. HANSEN, PH.D.  
5 COLUMBIA CIRCLE  
ALBANY, NY 12205

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MORLEY, John

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Additional names(s) of conveying party(ies) attached? ☐ Yes ☒ No

3. Nature of conveyance:

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☐ Merger

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☐ Change of Name

☐ Other \_\_\_\_\_

Street Address: 33 Locke Drive

City: Marlborough State: MA ZIP: 01752

Execution Date: June 20, 1996 and June 24, 1996

Additional name(s) & address(es) attached? ☐ Yes ☒ No

4. Application number(s) or registration numbers(s):

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08/613,382

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5. Name and address of party to whom correspondence concerning document should be mailed:

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6. Total number of applications and patents involved: 1

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Signature

July 2, 1996

Date

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PATENT

REEL: 8018 FRAME: 0813

MDA 7-5-96

ASSIGNMENT

WHEREAS, We, GUNNAR ABERG, a citizen of Sweden and JOHN MORLEY, a citizen of Great Britain, residing at 6 Brickyard Lane, Westborough, Massachusetts 01681 and 13 Kenmore Close, Kent Road, Kew, Richmond-upon-Thames, United Kingdom, respectively, have invented certain new and useful improvements in METHODS AND COMPOSITIONS FOR TREATING PULMONARY DISORDERS USING OPTICALLY PURE (R,R)-FORMOTEROL, for which We have executed an application for Letters Patent of the United States, Serial Number 08/613,382, filed March 7, 1996; and

WHEREAS, Sepracor, Inc. having offices at 33 Locke Drive, Marlborough, Massachusetts 01752, is desirous of obtaining the entire right, title and interest in, to and under the said improvements and the said application;

NOW, THEREFORE, in consideration of the sum of One Dollar (\$1.00) to us in hand paid, and other good and valuable consideration, the receipt of which is hereby acknowledged, We the said Gunnar Aberg and John Morley have sold, assigned, transferred and set over, and by these presents do hereby sell, assign, transfer and set over, unto the said Sepracor, Inc., its successors, legal representatives and assigns, the entire right, title and interest in, to and under the said improvements, and the said provisional application, all non-provisional applications arising therefrom, and all divisions, renewals and continuations thereof, and all Letters Patent which may be granted thereon and all reissues and extensions thereof, and all applications for Letters Patent which may hereafter be filed for said improvements in any country or countries foreign to the United States, and all Letters Patent which may be granted for said improvements in any country or countries foreign to the United States and all extensions, renewals and reissues thereof; and We hereby authorize and request the Commissioner of Patents of the United States, and any Official of any country or countries foreign to the United States, whose duty it is to issue patents on applications as aforesaid, to issue all Letters Patent for said improvements to the said Sepracor, Inc., its successors, legal representatives and assigns, in accordance with the terms of this instrument.

AND WE HEREBY covenant that We have full right to convey the entire interest herein assigned, and that We have not executed, and will not execute, any agreement in conflict herewith.

AND WE HEREBY further covenant and agree that We will communicate to the said Sepracor, Inc., its successors, legal representatives and assigns, any facts known to us respecting said improvements, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuing and reissue applications, make all rightful oaths and generally do everything

PATENT

REEL: 8018 FRAME: 0814

possible to aid the said Sepracor, Inc., its successors, legal representatives and assigns, to obtain and enforce proper patent protection for said improvements in all countries.

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 20<sup>th</sup> day of June, 1996.

  
\_\_\_\_\_  
GUNNAR ABERG

STATE OF MASSACHUSETTS )  
COUNTY OF Middlesex ) ss.:

On this 20<sup>th</sup> day of June, 1996, before me personally came GUNNAR ABERG, to me known and known to me to be the person of that name, who signed and sealed the foregoing instrument, and he acknowledged the same to be his free act and deed.

  
\_\_\_\_\_  
Notary Public

LINDA S. KING  
Notary Public  
My Commission Expires June 21, 2002

PATENT  
REEL: 8018 FRAME: 0815

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this  
24 day of June, 1996.

J. M.  
JOHN MORLEY

John R. McCallister 24/06/96  
Witness

P. L. [Signature] 24.06.96  
Witness

C



# BROVANA™

## (arformoterol tartrate) Inhalation Solution

15 mcg\*/2 mL

\*potency expressed as arformoterol

For oral inhalation only

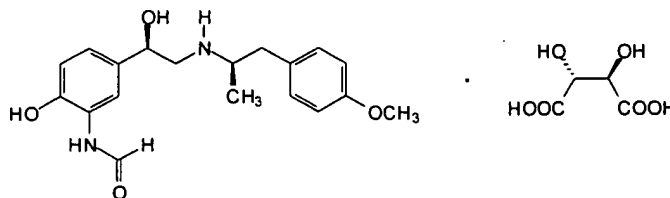
### WARNING:

Long-acting beta<sub>2</sub>-adrenergic agonists may increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta<sub>2</sub>-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol may apply to arformoterol (a long-acting beta<sub>2</sub>-adrenergic agonist), the active ingredient in BROVANA (see WARNINGS).

### DESCRIPTION

BROVANA (arformoterol tartrate) Inhalation Solution is a sterile, clear, colorless, aqueous solution of the tartrate salt of arformoterol, the (R,R)-enantiomer of formoterol.

Arformoterol is a selective beta<sub>2</sub>-adrenergic bronchodilator. The chemical name for arformoterol tartrate is formamide, N-[2-hydroxy-5-[(1R)-1-hydroxy-2-[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-, (2R,3R)-2,3-dihydroxybutanedioate (1:1 salt), and its established structural formula is as follows:



The molecular weight of *arformoterol tartrate* is 494.5 g/mol, and its empirical formula is C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>·C<sub>4</sub>H<sub>6</sub>O<sub>6</sub> (1:1 salt). It is a white to off-white solid that is slightly soluble in water.

Arformoterol tartrate is the United States Adopted Name (USAN) for (R,R)-formoterol L-tartrate.



29 BROVANA is supplied as 2 mL of arformoterol tartrate solution packaged in 2.1 mL  
30 unit-dose, low-density polyethylene (LDPE) vials. Each unit-dose vial contains 15 mcg  
31 of arformoterol (equivalent to 22 mcg of arformoterol tartrate) in a sterile, isotonic saline  
32 solution, pH-adjusted to 5.0 with citric acid and sodium citrate.

33 BROVANA requires no dilution before administration by nebulization. Like all other  
34 nebulized treatments, the amount delivered to the lungs will depend upon patient factors,  
35 the nebulizer used, and compressor performance. Using the PARI LC PLUS® nebulizer  
36 (with mouthpiece) connected to a PARI DURA-NEB® 3000 compressor under *in vitro*  
37 conditions, the mean delivered dose from the mouthpiece (% nominal) was  
38 approximately 4.1 mcg (27.6%) at a mean flow rate of 3.3 L/min. The mean nebulization  
39 time was 6 minutes or less. BROVANA should be administered from a standard jet  
40 nebulizer at adequate flow rates via face mask or mouthpiece (see **Dosage and**  
41 **Administration**).

42 Patients should be carefully instructed on the correct use of this drug product (please refer  
43 to the accompanying **Medication Guide**).

44

## 45 **CLINICAL PHARMACOLOGY**

### 46 **Mechanism of Action**

47 Arformoterol, the (R,R)-enantiomer of formoterol, is a selective long-acting beta<sub>2</sub>-  
48 adrenergic receptor agonist (beta<sub>2</sub>-agonist) that has two-fold greater potency than racemic  
49 formoterol (which contains both the (S,S) and (R,R)-enantiomers). The (S,S)-enantiomer  
50 is about 1,000-fold less potent as a beta<sub>2</sub>-agonist than the (R,R)-enantiomer. While it is  
51 recognized that beta<sub>2</sub>-receptors are the predominant adrenergic receptors in bronchial  
52 smooth muscle and beta<sub>1</sub>-receptors are the predominant receptors in the heart, data  
53 indicate that there are also beta<sub>2</sub>-receptors in the human heart comprising 10% to 50% of  
54 the total beta-adrenergic receptors. The precise function of these receptors has not been  
55 established, but they raise the possibility that even highly selective beta<sub>2</sub>-agonists may  
56 have cardiac effects.

57 The pharmacologic effects of beta<sub>2</sub>-adrenoceptor agonist drugs, including arformoterol,  
58 are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme  
59 that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine  
60 monophosphate (cyclic AMP). Increased intracellular cyclic AMP levels cause  
61 relaxation of bronchial smooth muscle and inhibition of release of mediators of  
62 immediate hypersensitivity from cells, especially from mast cells.

63 *In vitro* tests show that arformoterol is an inhibitor of the release of mast cell mediators,  
64 such as histamine and leukotrienes, from the human lung. Arformoterol also inhibits  
65 histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits  
66 allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The  
67 relevance of these *in vitro* and animal findings to humans is unknown.

## 68     **Animal Pharmacology**

69     In animal studies investigating its cardiovascular effects, arformoterol induced dose-  
70     dependent increases in heart rate and decreases in blood pressure consistent with its  
71     pharmacology as a beta-adrenergic agonist. In dogs, at systemic exposures higher than  
72     anticipated clinically, arformoterol also induced exaggerated pharmacologic effects of a  
73     beta-adrenergic agonist on cardiac function as measured by electrocardiogram (sinus  
74     tachycardia, atrial premature beats, ventricular escape beats, PVCs).

75     Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the  
76     occurrence of arrhythmias and sudden death (with histologic evidence of myocardial  
77     necrosis) when beta-agonists and methylxanthines are administered concurrently. The  
78     clinical significance of these findings is unknown.

## 79     **Pharmacokinetics**

80     The pharmacokinetics (PK) of arformoterol have been investigated in healthy subjects,  
81     elderly subjects, renally and hepatically impaired subjects, and chronic obstructive  
82     pulmonary disease (COPD) patients following the nebulization of the recommended  
83     therapeutic dose and doses up to 96 mcg.

## 84     **Absorption**

85     In COPD patients administered 15 mcg arformoterol every 12 hours for 14 days, the  
86     mean steady-state peak (R,R)-formoterol plasma concentration ( $C_{max}$ ) and systemic  
87     exposure ( $AUC_{0-12h}$ ) were 4.3 pg/mL and 34.5 pg\*hr/mL, respectively. The median  
88     steady-state peak (R,R)-formoterol plasma concentration time ( $t_{max}$ ) was observed  
89     approximately one half hour after drug administration.

90     Systemic exposure to (R,R)-formoterol increased linearly with dose in COPD patients  
91     following arformoterol doses of 5 mcg, 15 mcg, or 25 mcg twice daily for 2 weeks or  
92     15 mcg, 25 mcg, or 50 mcg once daily for 2 weeks.

93     In a crossover study in patients with COPD, when arformoterol 15 mcg inhalation  
94     solution and 12 and 24 mcg formoterol fumarate inhalation powder (Foradil®  
95     Aerolizer™) was administered twice daily for 2 weeks, the accumulation index was  
96     approximately 2.5 based on the plasma (R,R)-formoterol concentrations in all three  
97     treatments. At steady state, geometric means of systemic exposure ( $AUC_{0-12h}$ ) to  
98     (R,R)-formoterol following 15 mcg of arformoterol inhalation solution and 12 mcg of  
99     formoterol fumarate inhalation powder were 39.33 pg\*hr/mL and 33.93 pg\*hr/mL,  
100     respectively (ratio 1.16; 90% CI 1.00, 1.35), while the geometric means of the  $C_{max}$  were  
101     4.30 pg/mL and 4.75 pg/mL, respectively (ratio 0.91; 90% CI 0.76, 1.09).

102     In a study in patients with asthma, treatment with arformoterol 50 mcg with pre- and  
103     post-treatment with activated charcoal resulted in a geometric mean decrease in  
104     (R,R)-formoterol  $AUC_{0-6h}$  by 27% and  $C_{max}$  by 23% as compared to treatment with  
105     arformoterol 50 mcg alone. This suggests that a substantial portion of systemic drug  
106     exposure is due to pulmonary absorption.

107 **Distribution**

108 The binding of arformoterol to human plasma proteins *in vitro* was 52-65% at  
109 concentrations of 0.25, 0.5 and 1.0 ng/mL of radiolabeled arformoterol. The  
110 concentrations of arformoterol used to assess the plasma protein binding were higher than  
111 those achieved in plasma following inhalation of multiple doses of 50 mcg arformoterol.

112 **Metabolism**

113 *In vitro* profiling studies in hepatocytes and liver microsomes have shown that  
114 arformoterol is primarily metabolized by direct conjugation (glucuronidation) and  
115 secondarily by O-demethylation. At least five human uridine  
116 diphosphoglucuronosyltransferase (UGT) isozymes catalyze arformoterol  
117 glucuronidation *in vitro*. Two cytochrome P450 isozymes (CYP2D6 and secondarily  
118 CYP2C19) catalyze the O-demethylation of arformoterol.

119 Arformoterol did not inhibit CYP1A2, CYP2A6, CYP2C9/10, CYP2C19, CYP2D6,  
120 CYP2E1, CYP3A4/5, or CYP4A9/11 enzymes at >1,000-fold higher concentrations than  
121 the expected peak plasma concentrations following a therapeutic dose.

122 Arformoterol was almost entirely metabolized following oral administration of 35 mcg of  
123 radiolabeled arformoterol in eight healthy subjects. Direct conjugation of arformoterol  
124 with glucuronic acid was the major metabolic pathway. Most of the drug-related material  
125 in plasma and urine was in the form of glucuronide or sulfate conjugates of arformoterol.  
126 O-Desmethylation and conjugates of the O-desmethyl metabolite were relatively minor  
127 metabolites accounting for less than 17% of the dose recovered in urine and feces.

128 **Elimination**

129 After administration of a single oral dose of radiolabeled arformoterol to eight healthy  
130 male subjects, 63% of the total radioactive dose was recovered in urine and 11% in feces  
131 within 48 hours. A total of 89% of the total radioactive dose was recovered within  
132 14 days, with 67% in urine and 22% in feces. Approximately 1% of the dose was  
133 recovered as unchanged arformoterol in urine over 14 days. Renal clearance was 8.9 L/hr  
134 for unchanged arformoterol in these subjects.

135 In COPD patients given 15 mcg inhaled arformoterol twice a day for 14 days, the mean  
136 terminal half-life of arformoterol was 26 hours.

137 **Special Populations**

138 **Gender**

139 A population PK analysis indicated that there was no effect of gender upon the  
140 pharmacokinetics of arformoterol.

141 **Race**

142 The influence of race on arformoterol pharmacokinetics was assessed using a population  
143 PK analysis and data from healthy subjects. There was no clinically significant impact of  
144 race upon the pharmacokinetic profile of arformoterol.

145   **Geriatric**

146   The pharmacokinetic profile of arformoterol in 24 elderly subjects (aged 65 years or  
147   older) was compared to a younger cohort of 24 subjects (18-45 years) that were matched  
148   for body weight and gender. No significant differences in systemic exposure (AUC and  
149   C<sub>max</sub>) were observed when the two groups were compared.

150   **Pediatric**

151   The pharmacokinetics of arformoterol have not been studied in pediatric subjects.

152   **Hepatic Impairment**

153   The pharmacokinetic profile of arformoterol was assessed in 24 subjects with mild,  
154   moderate, and severe hepatic impairment. The systemic exposure (C<sub>max</sub> and AUC) to  
155   arformoterol increased 1.3 to 2.4-fold in subjects with hepatic impairment compared to  
156   16 demographically matched healthy control subjects. No clear relationship between  
157   drug exposure and the severity of hepatic impairment was observed. BROVANA should  
158   be used cautiously in patients with hepatic impairment.

159   **Renal Impairment**

160   The impact of renal disease upon the pharmacokinetics of arformoterol was studied in  
161   24 subjects with mild, moderate, or severe renal impairment. Systemic exposure  
162   (AUC and C<sub>max</sub>) to arformoterol was similar in renally impaired patients compared with  
163   demographically matched healthy control subjects.

164   **Pharmacogenetics**

165   Arformoterol is eliminated through the action of multiple drug metabolizing enzymes.  
166   Direct glucuronidation of arformoterol is mediated by several UGT enzymes and is the  
167   primary elimination route. O-Desmethylation is a secondary route catalyzed by the CYP  
168   enzymes CYP2D6 and CYP2C19. In otherwise healthy subjects with reduced CYP2D6  
169   and/or UGT1A1 enzyme activity, there was no impact on systemic exposure to  
170   arformoterol compared to subjects with normal CYP2D6 and/or UGT1A1 enzyme  
171   activities.

172   **Pharmacodynamics**

173   **Systemic Safety and Pharmacokinetic/ Pharmacodynamic Relationships**

174   The predominant adverse effects of inhaled beta<sub>2</sub>-agonists occur as a result of excessive  
175   activation of systemic beta-adrenergic receptors. The most common adverse effects may  
176   include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in plasma  
177   potassium, and increases in plasma glucose.

178   Effects on Serum Potassium and Serum Glucose Levels

179   Changes in serum potassium and serum glucose were evaluated in a dose ranging study  
180   of twice daily (5 mcg, 15 mcg, or 25 mcg; 215 patients with COPD) and once daily  
181   (15 mcg, 25 mcg, or 50 mcg; 191 patients with COPD) BROVANA in COPD patients.  
182   At 2 and 6 hours post dose at week 0 (after the first dose), mean changes in serum  
183   potassium ranging from 0 to -0.3 mEq/L were observed in the BROVANA groups with  
184   similar changes observed after 2 weeks of treatment. Changes in mean serum glucose

185 levels, ranging from a decrease of 1.2 mg/dL to an increase of 32.8 mg/dL were observed  
186 for BROVANA dose groups at both 2 and 6 hours post dose, both after the first dose and  
187 14 days of daily treatment.

#### 188 Electrophysiology

189 The effect of BROVANA on QT interval was evaluated in a dose ranging study  
190 following multiple doses of BROVANA 5 mcg, 15 mcg, or 25 mcg twice daily or  
191 15 mcg, 25 mcg, or 50 mcg once daily for 2 weeks in patients with COPD. ECG  
192 assessments were performed at baseline, time of peak plasma concentration and  
193 throughout the dosing interval. Different methods of correcting for heart rate were  
194 employed, including a subject-specific method and the Fridericia method.

195 Relative to placebo, the mean change in subject-specific QT<sub>c</sub> averaged over the dosing  
196 interval ranged from -1.8 to 2.7 msec, indicating little effect of BROVANA on cardiac  
197 repolarization after 2 weeks of treatment. The maximum mean change in subject-specific  
198 QT<sub>c</sub> for the BROVANA 15 mcg twice daily dose was 17.3 msec, compared with  
199 15.4 msec in the placebo group. No apparent correlation of QT<sub>c</sub> with arformoterol  
200 plasma-concentration was observed.

#### 201 **Electrocardiographic Monitoring in Patients with COPD**

202 The effect of different doses of BROVANA on cardiac rhythm was assessed using  
203 24-hour Holter monitoring in two 12-week double-blind, placebo-controlled studies of  
204 1,456 patients with COPD (873 received BROVANA at 15 or 25 mcg twice daily or  
205 50 mcg once daily doses; 293 received placebo; 290 received salmeterol). The 24-hour  
206 Holter monitoring occurred once at baseline, and up to 3 times during the 12-week  
207 treatment period. The rates of new-onset cardiac arrhythmias not present at baseline over  
208 the double-blind 12-week treatment period were similar (approximately 33-34%) for  
209 patients who received BROVANA 15 mcg twice daily to those who received placebo.  
210 There was a dose-related increase in new, treatment emergent arrhythmias seen in  
211 patients who received BROVANA 25 mcg twice daily and 50 mcg once daily, 37.6% and  
212 40.1 %, respectively. The frequencies of new treatment emergent events of non-  
213 sustained (3-10 beat run) and sustained (>10 beat run) ventricular tachycardia were 7.4%  
214 and 1.1% in BROVANA 15 mcg twice daily and 6.9% and 1.0% in placebo. In patients  
215 who received BROVANA 25 mcg twice daily and 50 mcg once daily the frequencies of  
216 non-sustained (6.2% and 8.2%, respectively) and sustained ventricular tachycardia (1.0%  
217 and 1.0%, respectively) were similar. Five cases of ventricular tachycardia were reported  
218 as adverse events (1 in BROVANA 15 mcg twice daily and 4 in placebo), with two of  
219 these events leading to discontinuation of treatment (2 in placebo).

220 There were no baseline occurrences of atrial fibrillation/ flutter observed on 24-hour  
221 Holter monitoring in patients treated with BROVANA 15 mcg twice daily or placebo.  
222 New, treatment emergent atrial fibrillation/ flutter occurred in 0.4% of patients who  
223 received BROVANA 15 mcg twice daily and 0.3% of patients who received placebo.  
224 There was a dose-related increase in the frequency of atrial fibrillation/ flutter reported in  
225 the BROVANA 25 mcg twice daily and 50 mcg once daily dose groups of 0.7% and  
226 1.4%, respectively. Two cases of atrial fibrillation/ flutter were reported as adverse  
227 events (1 in BROVANA 15 mcg twice daily and 1 in placebo).

228 Dose-related increases in mean maximum change in heart rate in the 12 hours after  
229 dosing were also observed following 12 weeks of dosing with BROVANA 15 mcg twice  
230 daily (8.8 bpm), 25 mcg twice daily (9.9 bpm) and 50 mcg once daily (12 bpm) versus  
231 placebo (8.5 bpm).

## 232 **Tachyphylaxis/ Tolerance**

233 In two placebo-controlled clinical trials in patients with COPD involving approximately  
234 725 patients in each, the overall efficacy of BROVANA was maintained throughout the  
235 12-week trial duration. However, tolerance to the bronchodilator effect of BROVANA  
236 was observed after 6 weeks of dosing, evidenced by a decrease in bronchodilator effect as  
237 measured by FEV<sub>1</sub>. FEV<sub>1</sub> improvement at the end of the 12-hour dosing interval  
238 decreased by approximately one third (22.1% mean improvement after the first dose  
239 compared to 14.6% at week 12). Tolerance to the FEV<sub>1</sub> bronchodilator effect of  
240 BROVANA was not accompanied by other clinical manifestations of tolerance in these  
241 trials.

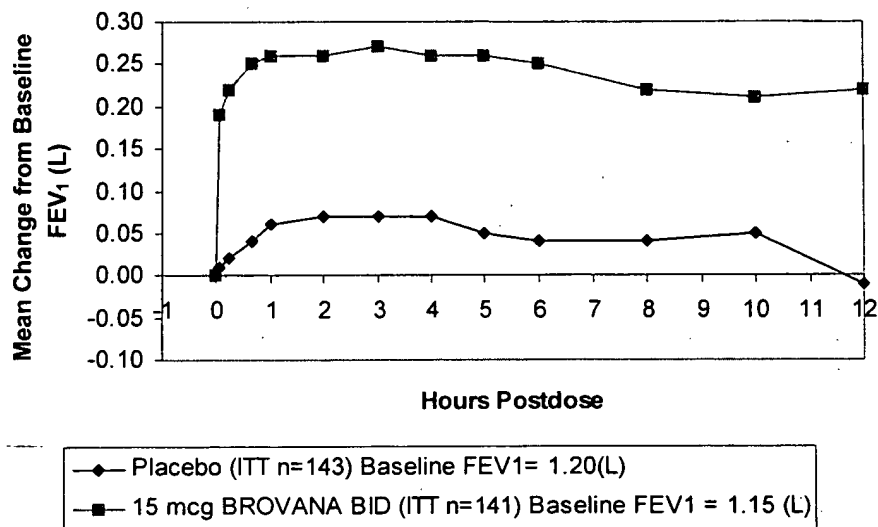
## 242 **CLINICAL TRIALS**

### 243 **Adult COPD Trials**

244 BROVANA (arformoterol tartrate) Inhalation Solution was studied in two identical,  
245 12-week, double-blind, placebo- and active-controlled, randomized, multi-center, parallel  
246 group trials conducted in the United States (Clinical Trial A and Clinical Trial B). A  
247 total of 1,456 adult patients (age range: 34 to 89 years; mean age: 63 years) with COPD  
248 who had a mean FEV<sub>1</sub> of 1.3 L (42% of predicted) were enrolled in the two clinical trials.  
249 The diagnosis of COPD was based on a prior clinical diagnosis of COPD, a smoking  
250 history (greater than 15 pack-years), age (at least 35 years), spirometry results (baseline  
251 FEV<sub>1</sub> ≤ 65% of predicted value and >0.70 L, and a FEV<sub>1</sub>/ forced vital capacity (FVC)  
252 ratio ≤ 70%). About 80% of patients in these studies had bronchodilator reversibility,  
253 defined as a 10% or greater increase FEV<sub>1</sub> after inhalation of 2 actuations (180 mcg)  
254 racemic albuterol from a metered dose inhaler). Both trials compared BROVANA  
255 15 mcg twice daily (288 patients), 25 mcg twice daily (292 patients), 50 mcg once daily  
256 (293 patients) with placebo (293 subjects). Both trials included salmeterol inhalation  
257 aerosol, 42 mcg twice daily as an active comparator (290 patients).

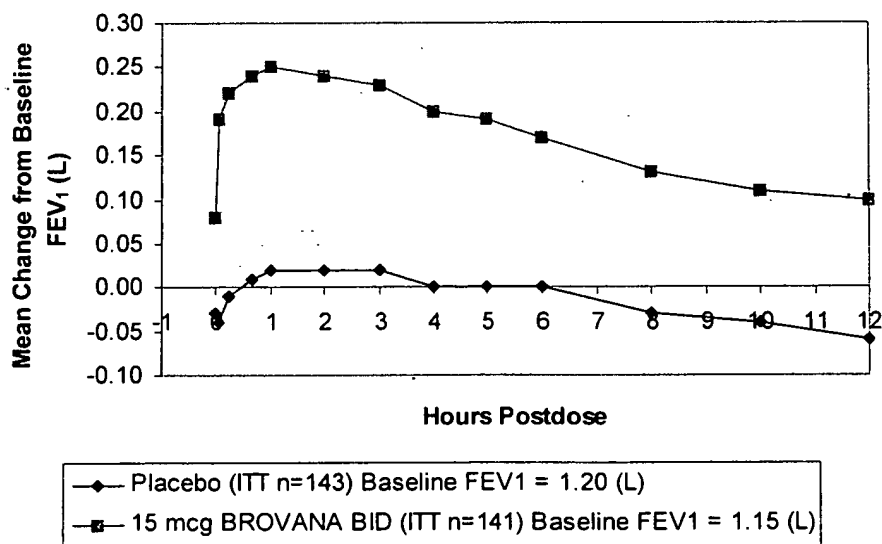
258 In both 12-week trials, BROVANA 15 mcg twice daily resulted in significantly greater  
259 post-dose bronchodilation (as measured by percent change from study baseline FEV<sub>1</sub> at  
260 the end of the dosing interval over the 12 weeks of treatment, the primary efficacy  
261 endpoint) compared to placebo. Compared to BROVANA 15 mcg twice daily,  
262 BROVANA 25 mcg twice daily and 50 mcg once daily did not provide sufficient  
263 additional benefit on a variety of endpoints, including FEV<sub>1</sub>, to support the use of higher  
264 doses. Plots of the mean change in FEV<sub>1</sub> values obtained over the 12 hours after dosing  
265 for the BROVANA 15 mcg twice daily dose group and for the placebo group are  
266 provided in Figures 1 and 2 for Clinical Trial A, below. The plots include mean FEV<sub>1</sub>  
267 change observed after the first dose and after 12 weeks of treatment. The results from  
268 Clinical Trial B were similar.

**Figure 1 Mean Change in FEV<sub>1</sub> Over Time for Clinical Trial A at Week 0 (Day 1)**



269

**Figure 2 Mean Change in FEV<sub>1</sub> Over Time for Clinical Trial A at Week 12**



270

271 BROVANA 15 mcg twice daily significantly improved bronchodilation compared to  
 272 placebo over the 12 hours after dosing (FEV<sub>1</sub> AUC<sub>0-12h</sub>). This improvement was  
 273 maintained over the 12 week study period.

274 Following the first dose of BROVANA 15 mcg, the median time to onset of  
275 bronchodilation, defined by an FEV<sub>1</sub> increase of 15%, occurred at 6.7 min. When  
276 defined as an increase in FEV<sub>1</sub> of 12% and 200 mL, the time to onset of bronchodilation  
277 was 20 min after dosing. Peak bronchodilator effect was generally seen within 1-3 hours  
278 of dosing.

279 In both clinical trials, compared to placebo, patients treated with BROVANA  
280 demonstrated improvements in peak expiratory flow rates, supplemental ipratropium and  
281 rescue albuterol use.

## 282 INDICATIONS AND USAGE

283 BROVANA (arformoterol tartrate) Inhalation Solution is indicated for the long term,  
284 twice daily (morning and evening) maintenance treatment of bronchoconstriction in  
285 patients with chronic obstructive pulmonary disease (COPD), including chronic  
286 bronchitis and emphysema. BROVANA is for use by nebulization only.

## 287 CONTRAINDICATIONS

288 BROVANA (arformoterol tartrate) Inhalation Solution is contraindicated in patients with  
289 a history of hypersensitivity to arformoterol, racemic formoterol or to any other  
290 components of this product.

## 291 WARNINGS

- 292 • **Long-acting beta<sub>2</sub>-adrenergic agonists may increase the risk of asthma-**  
293 **related death.**
  - 294 ○ A 28-week, placebo-controlled US study comparing the safety of salmeterol  
295 with placebo, each added to usual asthma therapy, showed an increase in  
296 asthma-related deaths in patients receiving salmeterol (13/13,176 in patients  
297 treated with salmeterol vs. 3/13,179 in patients treated with placebo; RR 4.37,  
298 95% CI 1.25, 15.34). The increased risk of asthma-related death may  
299 represent a class effect of the long-acting beta<sub>2</sub>-adrenergic agonists, including  
300 BROVANA. No study adequate to determine whether the rate of asthma  
301 related death is increased in patients treated with BROVANA has been  
302 conducted.
  - 303 ○ Clinical studies with racemic formoterol (Foradil® Aerolizer™) suggested a  
304 higher incidence of serious asthma exacerbations in patients who received  
305 racemic formoterol than in those who received placebo. The sizes of these  
306 studies were not adequate to precisely quantify the differences in serious  
307 asthma exacerbation rates between treatment groups.
- 308 • **The studies described above enrolled patients with asthma. Data are not**  
309 **available to determine whether the rate of death in patients with COPD is**  
310 **increased by long-acting beta<sub>2</sub>-adrenergic agonists.**
- 311 • **BROVANA is indicated for the long term, twice daily (morning and evening)**  
312 **maintenance treatment for bronchoconstriction in chronic obstructive**



- 313 pulmonary disease (COPD), and is not indicated for the treatment of acute  
314 episodes of bronchospasm, i.e., rescue therapy.
- 315 • BROVANA should not be initiated in patients with acutely deteriorating COPD,  
316 which may be a life-threatening condition. The use of BROVANA in this setting  
317 is inappropriate.
  - 318 • BROVANA should not be used in children as the safety and efficacy of  
319 BROVANA have not been established in pediatric patients.
  - 320 • BROVANA should not be used in conjunction with other inhaled, long-acting  
321 beta<sub>2</sub>-agonists. BROVANA should not be used with other medications  
322 containing long-acting beta<sub>2</sub>-agonists.
  - 323 • When beginning treatment with BROVANA, patients who have been taking  
324 inhaled, short-acting beta<sub>2</sub>-agonists on a regular basis (e.g., four times a day)  
325 should be instructed to discontinue the regular use of these drugs and use them  
326 only for symptomatic relief of acute respiratory symptoms.
  - 327 • See PRECAUTIONS, Information for Patients and the accompanying  
328 Medication Guide.

### 329 Paradoxical Bronchospasm

330 As with other inhaled beta<sub>2</sub>-agonists, BROVANA can produce paradoxical bronchospasm  
331 that may be life-threatening. If paradoxical bronchospasm occurs, BROVANA should be  
332 discontinued immediately and alternative therapy instituted.

### 333 Deterioration of Disease

334 COPD may deteriorate acutely over a period of hours or chronically over several days or  
335 longer. If BROVANA no longer controls the symptoms of bronchoconstriction, or the  
336 patient's inhaled, short-acting beta<sub>2</sub>-agonist becomes less effective or the patient needs  
337 more inhalation of short-acting beta<sub>2</sub>-agonist than usual, these may be markers of  
338 deterioration of disease. In this setting, a re-evaluation of the patient and the COPD  
339 treatment regimen should be undertaken at once. Increasing the daily dosage of  
340 BROVANA beyond the recommended 15 mcg twice daily dose is not appropriate in this  
341 situation.

### 342 Cardiovascular Effects

343 BROVANA, like other beta<sub>2</sub>-agonists, can produce a clinically significant cardiovascular  
344 effect in some patients as measured by increases in pulse rate, blood pressure, and/or  
345 symptoms. Although such effects are uncommon after administration of BROVANA at  
346 the recommended dose, if they occur, the drug may need to be discontinued. In addition,  
347 beta-agonists have been reported to produce ECG changes, such as flattening of the  
348 T wave, prolongation of the QTc interval, and ST segment depression. The clinical  
349 significance of these findings is unknown. BROVANA, as with other sympathomimetic  
350 amines, should be used with caution in patients with cardiovascular disorders, especially  
351 coronary insufficiency, cardiac arrhythmias, and hypertension (see PRECAUTIONS,  
352 General).

353 **Immediate Hypersensitivity Reactions**

354 Immediate hypersensitivity reactions may occur after administration of BROVANA as  
355 demonstrated by cases of anaphylactic reaction, urticaria, angioedema, rash and  
356 bronchospasm.

357 **Do Not Exceed Recommended Dose**

358 Fatalities have been reported in association with excessive use of inhaled  
359 sympathomimetic drugs. As with other inhaled beta<sub>2</sub>-adrenergic drugs, BROVANA  
360 should not be used more often, at higher doses than recommended, or with other long-  
361 acting beta-agonists.

362 **PRECAUTIONS**

363 **General**

364 BROVANA (arformoterol tartrate) Inhalation Solution should not be used to treat acute  
365 symptoms of COPD. BROVANA has not been studied in the relief of acute symptoms  
366 and extra doses should not be used for that purpose. When prescribing BROVANA, the  
367 physician should also provide the patient with an inhaled, short-acting beta<sub>2</sub>-agonist for  
368 treatment of COPD symptoms that occur acutely, despite regular twice-daily (morning  
369 and evening) use of BROVANA. Patients should also be cautioned that increasing  
370 inhaled beta<sub>2</sub>-agonist use is a signal of deteriorating disease for which prompt medical  
371 attention is indicated (see **Information for Patients** and the accompanying **Medication**  
372 **Guide**).

373 BROVANA, like other sympathomimetic amines, should be used with caution in patients  
374 with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and  
375 hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who  
376 are unusually responsive to sympathomimetic amines. Clinically significant changes in  
377 systolic and/or diastolic blood pressure, pulse rate and electrocardiograms have been seen  
378 infrequently in individual patients in controlled clinical studies with arformoterol tartrate.  
379 Doses of the related beta<sub>2</sub>-agonist albuterol, when administered intravenously, have been  
380 reported to aggravate preexisting diabetes mellitus and ketoacidosis.

381 Beta-agonist medications may produce significant hypokalemia in some patients,  
382 possibly though intracellular shunting, which has the potential to produce adverse  
383 cardiovascular effects. The decrease in serum potassium is usually transient, not  
384 requiring supplementation.

385 Clinically significant changes in blood glucose and/or serum potassium were infrequent  
386 during clinical studies with long-term administration of BROVANA at the recommended  
387 dose.

388 **Information for Patients**

389 Patients should be instructed to read the accompanying **Medication Guide** with each  
390 new prescription and refill. The complete text of the **Medication Guide** is reprinted  
391 at the end of this document. Patients should be given the following information:

- 392 1. Patients should be informed that long-acting beta<sub>2</sub>-adrenergic agonists may increase  
393 the risk of asthma-related death.
- 394 2. BROVANA is not indicated to relieve acute respiratory symptoms and extra doses  
395 should not be used for that purpose. Acute symptoms should be treated with an  
396 inhaled, short-acting, beta<sub>2</sub>-agonist (the health-care provider should prescribe the  
397 patient with such medication and instruct the patient in how it should be used).  
398 Patients should be instructed to seek medical attention if their symptoms worsen, if  
399 BROVANA treatment becomes less effective, or if they need more inhalations of a  
400 short-acting beta<sub>2</sub>-agonist than usual. Patients should not inhale more than one dose  
401 at any one time. The daily dosage of BROVANA should not exceed one vial  
402 (15 mcg) by inhalation twice daily (30 mcg total daily dose).
- 403 3. Patients should be informed that treatment with beta<sub>2</sub>-agonists may lead to adverse  
404 events which include palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- 405 4. Patients should be instructed to use BROVANA by nebulizer only and not to inject or  
406 swallow this inhalation solution.
- 407 5. Patients should protect BROVANA single-use low-density polyethylene (LDPE)  
408 vials from light and excessive heat. The protective foil pouches should be stored  
409 under refrigeration between 2°C and 8°C (36°–46°F). They should not be used after  
410 the expiration date stamped on the container. Patients should be instructed that once  
411 the foil pouch is opened, the contents of the vial should be used immediately and to  
412 discard any vial if the solution is not colorless.
- 413 6. The drug compatibility (physical and chemical), efficacy and safety of BROVANA  
414 when mixed with other drugs in a nebulizer have not been established.
- 415 7. Women should be advised to contact their physician if they become pregnant or if  
416 they are nursing.
- 417 8. It is important that patients understand how to use the BROVANA appropriately and  
418 how it should be used in relation to other medications to treat COPD they are taking  
419 (see the accompanying Medication Guide and the Instructions for Using  
420 BROVANA).

## 421 **Drug Interactions**

422 If additional adrenergic drugs are to be administered by any route, they should be used  
423 with caution because the pharmacologically predictable sympathetic effects of  
424 BROVANA may be potentiated.

425 When paroxetine, a potent inhibitor of CYP2D6, was co-administered with BROVANA  
426 at steady-state, exposure to either drug was not altered. Dosage adjustments of  
427 BROVANA are not necessary when the drug is given concomitantly with potent  
428 CYP2D6 inhibitors.

429 Concomitant treatment with methylxanthines (aminophylline, theophylline), steroids, or  
430 diuretics may potentiate any hypokalemic effect of adrenergic agonists.

431 The ECG changes and/or hypokalemia that may result from the administration of non-  
432 potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened

433 by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded.  
434 Although the clinical significance of these effects is not known, caution is advised in the  
435 co-administration of beta-agonists with non-potassium sparing diuretics.

436 BROVANA, as with other beta<sub>2</sub>-agonists, should be administered with extreme caution to  
437 patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or  
438 drugs known to prolong the QT<sub>c</sub> interval because the action of adrenergic agonists on the  
439 cardiovascular system may be potentiated by these agents. Drugs that are known to  
440 prolong the QT<sub>c</sub> interval have an increased risk of ventricular arrhythmias. The  
441 concurrent use of intravenously or orally administered methylxanthines (e.g.,  
442 aminophylline, theophylline) by patients receiving BROVANA has not been completely  
443 evaluated. In two combined 12-week placebo controlled trials that included BROVANA  
444 doses of 15 mcg twice daily, 25 mcg twice daily, and 50 mcg once daily, 54 of 873  
445 BROVANA -treated subjects received concomitant theophylline at study entry. In a  
446 12-month controlled trial that included a 50 mcg once daily BROVANA dose, 30 of the  
447 528 BROVANA -treated subjects received concomitant theophylline at study entry. In  
448 these trials, heart rate and systolic blood pressure were approximately 2-3 bpm and  
449 6-8 mm Hg higher, respectively, in subjects on concomitant theophylline compared with  
450 the overall population.

451 Beta-adrenergic receptor antagonists (beta-blockers) and BROVANA may interfere with  
452 the effect of each other when administered concurrently. Beta-blockers not only block  
453 the therapeutic effects of beta-agonists, but may produce severe bronchospasm in COPD  
454 patients. Therefore, patients with COPD should not normally be treated with beta-  
455 blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial  
456 infarction, there may be no acceptable alternatives to the use of beta-blockers in patients  
457 with COPD. In this setting, cardioselective beta-blockers could be considered, although  
458 they should be administered with caution.

#### 459 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

460 Long-term studies were conducted in mice using oral administration and rats using  
461 inhalation administration to evaluate the carcinogenic potential of arformoterol.

462 In a 24-month carcinogenicity study in CD-1 mice, arformoterol caused a dose-related  
463 increase in the incidence of uterine and cervical endometrial stromal polyps and stromal  
464 cell sarcoma in female mice at oral doses of 1 mg/kg and above (AUC exposure  
465 approximately 70 times adult exposure at the maximum recommended daily inhalation  
466 dose).

467 In a 24-month carcinogenicity study in Sprague-Dawley rats, arformoterol caused a  
468 statistically significant increase in the incidence of thyroid gland c-cell adenoma and  
469 carcinoma in female rats at an inhalation dose of 200 mcg/kg (AUC exposure  
470 approximately 130 times adult exposure at the maximum recommended daily inhalation  
471 dose). There were no tumor findings with an inhalation dose of 40 mcg/kg (AUC  
472 exposure approximately 55 times adult exposure at the maximum recommended daily  
473 inhalation dose).

474 Arformoterol was not mutagenic or clastogenic in the following tests: mutagenicity tests  
475 in bacteria, chromosome aberration analyses in mammalian cells, and micronucleus test  
476 in mice.

477 Arformoterol had no effects on fertility and reproductive performance in rats at oral doses  
478 up to 10 mg/kg (approximately 2700 times the maximum recommended daily inhalation  
479 dose in adults on a mg/m<sup>2</sup> basis).

## 480 **Pregnancy: Teratogenic Effects**

### 481 **Pregnancy Category C**

482 Arformoterol has been shown to be teratogenic in rats based upon findings of  
483 omphalocele (umbilical hernia), a malformation, at oral doses of 1 mg/kg and above  
484 (AUC exposure approximately 370 times adult exposure at the maximum recommended  
485 daily inhalation dose). Increased pup loss at birth and during lactation and decreased pup  
486 weights were observed in rats at oral doses of 5 mg/kg and above (AUC exposure  
487 approximately 1100 times adult exposure at the maximum recommended daily inhalation  
488 dose). Delays in development were evident with an oral dose of 10 mg/kg (AUC  
489 exposure approximately 2400 times adult exposure at the maximum recommended daily  
490 inhalation dose).

491 Arformoterol has been shown to be teratogenic in rabbits based upon findings of  
492 malpositioned right kidney, a malformation, at oral doses of 20 mg/kg and above (AUC  
493 exposure approximately 8400 times adult exposure at the maximum recommended daily  
494 inhalation dose). Malformations including brachydactyly, bulbous aorta, and liver cysts  
495 were observed at doses of 40 mg/kg and above (approximately 22,000 times the  
496 maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis). Malformation  
497 including adactyly, lobular dysgenesis of the lung, and interventricular septal defect were  
498 observed at 80 mg/kg (approximately 43,000 times the maximum recommended daily  
499 inhalation dose in adults on a mg/m<sup>2</sup> basis). Embryo lethality was observed at  
500 80 mg/kg/day (approximately 43,000 times the maximum recommended daily inhalation  
501 dose in adults on a mg/m<sup>2</sup> basis). Decreased pup body weights were observed at doses of  
502 40 mg/kg/day and above (approximately 22,000 times the maximum recommended daily  
503 inhalation dose in adults on a mg/m<sup>2</sup> basis). There were no teratogenic findings in rabbits  
504 with oral dose of 10 mg/kg and lower (AUC exposure approximately 4900 times adult  
505 exposure at the maximum recommended daily inhalation dose).

506 There are no adequate and well-controlled studies in pregnant women. BROVANA  
507 should be used during pregnancy only if the potential benefit justifies the potential risk to  
508 the fetus.

### 509 **Use in Labor and Delivery**

510 There are no human studies that have investigated the effects of BROVANA on preterm  
511 labor or labor at term.

512 Because beta-agonists may potentially interfere with uterine contractility, BROVANA  
513 should be used during labor and delivery only if the potential benefit justifies the  
514 potential risk.

515 **Nursing Mothers**

516 In reproductive studies in rats, arformoterol was excreted in the milk. It is not known  
517 whether arformoterol is excreted in human milk. Because many drugs are excreted in  
518 human milk, caution should be exercised when BROVANA is administered to a nursing  
519 woman.

520 **Pediatric**

521 BROVANA is approved for use in the long term maintenance treatment of  
522 bronchoconstriction associated with chronic obstructive pulmonary disease, including  
523 chronic bronchitis and emphysema. This disease does not occur in children. The safety  
524 and effectiveness of BROVANA in pediatric patients have not been established.

525 **Geriatric**

526 Of the 873 patients who received BROVANA in two placebo-controlled clinical studies  
527 in adults with COPD, 391 (45%) were 65 years of age or older while 96 (11%) were  
528 75 years of age or older. No overall differences in safety or effectiveness were observed  
529 between these subjects and younger subjects. Among subjects age 65 years and older,  
530 129 (33%) received BROVANA at the recommended dose of 15 mcg twice daily, while  
531 the remainder received higher doses. ECG alerts for ventricular ectopy in patients 65 to  
532 ≤ 75 years of age were comparable among patients receiving 15 mcg twice daily, 25 mcg  
533 twice daily, and placebo (3.9%, 5.2%, and 7.1%, respectively). A higher frequency  
534 (12.4%) was observed when BROVANA was dosed at 50 mcg once daily. The clinical  
535 significance of this finding is not known. Other reported clinical experience has not  
536 identified differences in responses between the elderly and younger patients, but greater  
537 sensitivity of some older individuals cannot be ruled out.

538 **ADVERSE REACTIONS**

539 **Experience in Adult Patients with COPD**

540 Of the 1,456 COPD patients in the two 12-week, placebo-controlled trials, 288 were  
541 treated with BROVANA (arformoterol tartrate) inhalation solution 15 mcg twice daily  
542 and 293 were treated with placebo. Doses of 25 mcg twice daily and 50 mcg once daily  
543 were also evaluated. The numbers and percent of patients who reported adverse events  
544 were comparable in the 15 mcg twice daily and placebo groups.

545 The following table shows adverse events where the frequency was greater than or equal  
546 to 2% in the BROVANA 15 mcg twice daily group and where the rates of adverse events  
547 in the BROVANA 15 mcg twice daily group exceeded placebo. Ten adverse events  
548 demonstrated a dose relationship: asthenia, fever, bronchitis, COPD, headache, vomiting,  
549 hyperkalemia, leukocytosis, nervousness, and tremor.

**Table 1: Number of Patients Experiencing Adverse Events from Two 12 Week, Double-Blind, Placebo Controlled Clinical Trials**

	BROVANA 15 mcg twice daily		Placebo	
	n	(%)	n	(%)
	288	(100)	293	(100)
Total Patients				
Pain	23	(8)	16	(5)
Chest Pain	19	(7)	19	(6)
Back Pain	16	(6)	6	(2)
Diarrhea	16	(6)	13	(4)
Sinusitis	13	(5)	11	(4)
Leg Cramps	12	(4)	6	(2)
Dyspnea	11	(4)	7	(2)
Rash	11	(4)	5	(2)
Flu Syndrome	10	(3)	4	(1)
Peripheral Edema	8	(3)	7	(2)
Lung Disorder*	7	(2)	2	(1)

\* Reported terms coded to "Lung Disorder" were predominantly pulmonary or chest congestion.

551 Adverse events occurring in patients treated with BROVANA 15 mcg twice daily with a  
 552 frequency of <2%, but greater than placebo were as follows:

553 **Body as a Whole:** abscess, allergic reaction, digitalis intoxication, fever, hernia, injection  
 554 site pain, neck rigidity, neoplasm, pelvic pain, retroperitoneal hemorrhage

555 **Cardiovascular:** arteriosclerosis, atrial flutter, AV block, congestive heart failure, heart  
 556 block, myocardial infarct, QT interval prolonged, supraventricular tachycardia, inverted  
 557 T-wave

558 **Digestive:** constipation, gastritis, melena, oral moniliasis, periodontal abscess, rectal  
 559 hemorrhage

560 **Metabolic and Nutritional Disorders:** dehydration, edema, glucose tolerance decreased,  
 561 gout, hyperglycemia, hyperlipemia, hypoglycemia, hypokalemia

562 **Musculoskeletal:** arthralgia, arthritis, bone disorder, rheumatoid arthritis, tendinous  
 563 contracture

564 **Nervous:** agitation, cerebral infarct, circumoral paresthesia, hypokinesia, paralysis,  
 565 somnolence, tremor

566 **Respiratory:** carcinoma of the lung, respiratory disorder, voice alteration

567 **Skin and Appendages:** dry skin, herpes simplex, herpes zoster, skin discoloration, skin  
 568 hypertrophy

569 **Special Senses:** abnormal vision, glaucoma

570 **Urogenital:** breast neoplasm, calcium crystalluria, cystitis, glycosuria, hematuria, kidney  
 571 calculus, nocturia, PSA increase, pyuria, urinary tract disorder, urine abnormality.

572 Overall, the frequency of all cardiovascular adverse events for BROVANA in the two,  
 573 placebo controlled trials was low and comparable to placebo (6.9% in BROVANA  
 574 15 mcg twice daily and 13.3% in the placebo group). There were no frequently occurring  
 575 specific cardiovascular adverse events for BROVANA (frequency  $\geq 1\%$  and greater than  
 576 placebo). The rate of COPD exacerbations was also comparable between the  
 577 BROVANA 15 mcg twice daily and placebo groups, 12.2% and 15.1%, respectively.

578 Other adverse reactions which may occur with selective beta<sub>2</sub>-adrenoceptor agonists such  
 579 as BROVANA; include angina, hypertension or hypotension, tachycardia, arrhythmias,  
 580 nervousness, headache, tremor, dry mouth, palpitation, muscle cramps, nausea, dizziness,  
 581 fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis and insomnia.

## 582 **Drug Abuse and Dependence**

583 There were no reported cases of abuse or evidence of drug dependence with the use of  
 584 BROVANA in the clinical trials.

## 585 **OVERDOSAGE**

586 The expected signs and symptoms associated with overdosage of BROVANA  
 587 (arformoterol tartrate) Inhalation Solution are those of excessive beta-adrenergic  
 588 stimulation and/or occurrence or exaggeration of any of the signs and symptoms listed  
 589 under **ADVERSE REACTIONS**, e.g., angina, hypertension or hypotension, tachycardia,



590 with rates up to 200 bpm, arrhythmias, nervousness, headache, tremor, dry mouth,  
591 palpitation, muscle cramps, nausea, dizziness, fatigue, malaise, hypokalemia,  
592 hyperglycemia, metabolic acidosis and insomnia. As with all inhaled sympathomimetic  
593 medications, cardiac arrest and even death may be associated with an overdose of  
594 BROVANA.

595 Treatment of overdosage consists of discontinuation of BROVANA together with  
596 institution of appropriate symptomatic and/or supportive therapy. The judicious use of a  
597 cardioselective beta-receptor blocker may be considered, bearing in mind that such  
598 medication can produce bronchospasm. There is insufficient evidence to determine if  
599 dialysis is beneficial for overdosage of BROVANA. Cardiac monitoring is  
600 recommended in cases of overdosage.

601 Clinical signs in dogs included flushing of the body surface and facial area, reddening of  
602 the ears and gums, tremor, and increased heart rate. A death was reported in dogs after a  
603 single oral dose of 5 mg/kg (approximately 4500 times the maximum recommended daily  
604 inhalation dose in adults on a mg/m<sup>2</sup> basis). Death occurred for a rat that received  
605 arformoterol at a single inhalation dose of 1600 mcg/kg (approximately 430 times the  
606 maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis).

## 607 **DOSAGE AND ADMINISTRATION**

608 The recommended dose of BROVANA (arformoterol tartrate) Inhalation Solution for  
609 COPD patients is 15 mcg administered twice a day (morning and evening) by  
610 nebulization. A total daily dose greater than 30 mcg (15 mcg twice daily) is not  
611 recommended. BROVANA should be administered by the inhaled route via a standard  
612 jet nebulizer connected to an air compressor (see the accompanying **Medication Guide**).  
613 BROVANA should not be swallowed. BROVANA should be stored refrigerated in  
614 individual unit dose, low-density polyethylene (LDPE) vials sealed in single foil pouches.  
615 Vials should be removed from the foil pouches and used immediately after opening.

616 If the recommended maintenance treatment regimen fails to provide the usual response,  
617 medical advice should be sought immediately, as this is often a sign of destabilization of  
618 COPD. Under these circumstances, the therapeutic regimen should be re-evaluated and  
619 additional therapeutic options should be considered.

620 No dose adjustment is required for patients with renal or hepatic impairment. However,  
621 since the clearance of BROVANA is prolonged in patients with hepatic impairment, they  
622 should be monitored closely.

623 The drug compatibility (physical and chemical), efficacy, and safety of BROVANA  
624 when mixed with other drugs in a nebulizer have not been established.

625 The safety and efficacy of BROVANA have been established in clinical trials when  
626 administered using the PARI LC PLUS<sup>®</sup> nebulizers and PARI DURA-NEB<sup>®</sup> 3000  
627 compressors. The safety and efficacy of BROVANA when administered using other  
628 nebulizer systems has not been established.

629

630 **HOW SUPPLIED**

631 BROVANA (arformoterol tartrate) Inhalation Solution is supplied in a single strength  
632 (15 mcg of arformoterol, equivalent to 22 mcg of arformoterol tartrate) as 2 mL of a  
633 sterile solution in unit-dose, low-density polyethylene (LDPE) vials individually  
634 overwrapped in foil. BROVANA is available in a shelf-carton containing 30 or 60  
635 individually pouched vials.

636 NDC 63402-911-30: carton of 30 unit-dose individually pouched vials.

637 NDC 63402-911-60: carton of 60 unit-dose individually pouched vials.

638

639 **CAUTION:** Federal law (U.S.) prohibits dispensing without prescription.

640 **Storage**

641 Store BROVANA in the protective foil pouch under refrigeration at 36°-46°F (2°-8°C).  
642 Protect from light and excessive heat. Once the foil pouch is opened, the contents of the  
643 vial should be used immediately. Discard any vial if the solution is not colorless.

644 Unopened foil pouches of BROVANA can also be stored at room temperature 68°-77°F,  
645 (20°-25°C) for up to 6 weeks. If stored at room temperature, discard if not used after  
646 6 weeks or if past the expiration date, whichever is sooner.

647



648

649 Manufactured for:

650 **Sepracor Inc.**

651 Marlborough, MA 01752 USA

652 For customer service, call 1-888-394-7377.

653 To report adverse events, call 1-877-737-7226.

654 For medical information, call 1-800-739-0565.

655

656 October 2006

657 Code XXXX

D



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-912

Sepracor Inc.  
84 Waterford Drive  
Marlborough, MA 01752-7010

Attention: Renee M. Carroll, M.S., RAC  
Associate Director, Regulatory Affairs

Dear Ms. Carroll:

Please refer to your new drug application (NDA) dated December 8, 2005, received December 12, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brovana (arformoterol tartrate) Inhalation Solution.

We acknowledge receipt of your submissions dated December 20, 2005, and January 3, and 6, February 14, 16, and 22, March 23, 29, and 31, April 11, 18, and 27, May 15, June 7, 15, 16, and 23, July 12, 13, and 21, August 3, 24, 28, and 29, September 6, 12, 19, 20, 27, and 28, and October 2, 4, and 5, 2006.

This new drug application provides for the use of Brovana (arformoterol tartrate) Inhalation Solution for the treatment of bronchoconstriction associated with chronic obstructive pulmonary disease.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, Medication Guide) submitted on October 5, 2006, (immediate container and carton labels) submitted on October 4, 2006. Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-912.**" Approval of this submission by FDA is not required before the labeling is used.

Within 30 days of the date of this letter, submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the labeling text submitted on October 5, 2006. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

We remind you of your postmarketing study commitment(s) in your submission dated October 4, 2006. These commitments are listed below.

1. Conduct a multicenter, randomized, placebo-controlled, large, simple safety trial to evaluate the effects of long term use of BROVANA (arformoterol tartrate) Inhalation Solution in patients with COPD. The objective of this trial is to determine the risk of fatal and life-threatening respiratory events associated with the long term use of BROVANA in patients with COPD. The trial will be of adequate size and duration to meet the objective. The final study report will be submitted as a supplement.

Protocol Submission Date: August 2007  
Study Start Date: December 2007  
Final Report Submission Date: December 2012

2. Conduct a safety and tolerability study with one or more doses and one or more dose levels of BROVANA (arformoterol tartrate) Inhalation Solution in children with asthma and/or obstructive airway disease. The objective of this study is to assess the safety and tolerability of BROVANA in children 12 years of age and younger with asthma. The study will include a placebo or active control treatment group, as appropriate. The study will also include children age 12 years and younger so that the lower age limit is based upon the age at which asthma/obstructive airway disease exists. The trial will be of adequate size and duration to meet the objective. The final study report will be submitted as a supplement.

Protocol Submission Date: June 2007  
Study Start Date: September 2007  
Final Report Submission Date: December 2008

3. Conduct a safety and efficacy study with one or more doses and one or more dose levels of BROVANA (arformoterol tartrate) Inhalation Solution in children with asthma and/or obstructive airway disease presenting with an acute exacerbation. The objective of this study is to establish the safety and efficacy of BROVANA in children 12 years of age and younger with an acute exacerbation of asthma. The study will include a placebo or active control treatment group, as appropriate. The study will also include children age 12 years and younger so that the lower age limit is based upon the age at which asthma/obstructive airway disease exists. The trial will be of adequate size and duration to meet the objective. The final study report will be submitted as a supplement.

Protocol Submission Date: September 2008  
Study Start Date: January 2009  
Final Report Submission Date: May 2011

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled

**“Postmarketing Study Commitment Protocol”, “Postmarketing Study Commitment Final Report”, or “Postmarketing Study Commitment Correspondence.”**

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Pulmonary and Allergy Products, and two copies of both the promotional materials and the package insert(s) directly to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

We also remind you of the following Chemistry, Manufacturing, and Controls (CMC) agreements listed in your submission dated September 12, 2006.

1. Submit the validation report for method (b) (4) to the Agency upon completion and prior to commercialization of Brovana Inhalation Solution.
2. Conduct further extractable studies of the foil and submit the data to the NDA.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 301-796-1231.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Director  
Division of Pulmonary and Allergy Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure: PKG Insert, Medguide

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

-----  
Badrul Chowdhury  
10/6/2006 03:01:19 PM

E







**Terminal Disclaimer To Obviate A Double  
Patenting Rejection Over A Prior Patent**

Docket No.  
0701.001F

In Re Application Of:

ABERG et al.

Serial No.  
09/927,008

Filing Date  
August 9, 2001

Examiner  
Haghighatian, M.

Group Art Unit  
1616

Invention: **METHODS AND COMPOSITIONS FOR TREATING PULMONARY DISORDERS USING OPTICALLY  
PURE ( R,R) FORMOTEROL**

Owner of Record: **SEPRACOR, INC.**

RECEIVED  
DEC 12 2002  
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TO THE ASSISTANT COMMISSIONER FOR PATENTS:

The above-identified owner of record of a 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173, as presently shortened by any terminal disclaimer, of prior Patent No. US 5,795,564 . The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors and/or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it later expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of an organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney of record.

  
Signature

Dated: December 5, 2002

Candice J. Clement, Esq.  
Typed or Printed Name

12/11/2002 CCHAU1 00000123 09927008

03 FC:1814

110.00 OP

- ☒ Terminal disclaimer fee under 37 C.F.R. 1.20(d) included.  
☒ PTO suggested wording for terminal disclaimer was unchanged.  
☐ Certification under 37 C.F.R. 3.73(b) is required if terminal disclaimer is signed by the assignee.

R



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<b>Patent Bibliographic Data</b>		<b>11/16/2006 11:26 AM</b>	
Patent Number:	6589508	Application Number:	09927008
Issue Date:	07/08/2003	Filing Date:	08/09/2001
Title: METHODS AND COMPOSITIONS FOR TREATING PULMONARY DISORDERS USING OPTICA			
Status:	8th year fee window opens: 07/08/2010		Entity: Large
Window Opens:	07/08/2010	Surcharge Date:	01/11/2011
Fee Amt Due:	Window not open	Surchg Amt Due:	Window not open
Fee Code:	1552	MAINTENANCE FEE DUE AT 7.5 YEARS	
Surcharge Fee Code:			
Most recent events (up to 7):	Payment of Maintenance Fee, 4th Year, Large Entity. --- End of Maintenance History ---		
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G



**Selected Activities for  
BROVANA™ Regulatory Review**

<b>Date</b>	<b>Type</b>	<b>Activity</b>
2-20-98	IND	IND Application (7 volumes)
2-27-98	IND	Communication from FDA to Sepracor: Assigned IND# 55,302 for (R,R) –formoterol tartrate. Notated other identifying data for the application.
3-2-98 (A)	IND	Communication from Sepracor to FDA regarding correction to the 2-27-98 letter from the FDA Re: 55,302.
3-2-98 (B)	IND	Communication from Sepracor to FDA regarding request for comparison of 2-98 & 12-97 versions of 091-003
3-4-98	IND	Response to 091-003 questions
3-20-98	IND	Request by FDA for additional one-month and three-month stability data on the drug product
3-23-98	IND	Submission: IND – stability data for drug product
3-24-98 (A)	IND	Submission: IND – stability data for drug product
3-24-98 (B)	IND	Communication from Sepracor to FDA regarding container closure system
3-25-98	IND	Communication from Sepracor to FDA regarding 20 mL bottle data-White Colorant information
3-26-98 (A)	IND	Request by FDA regarding pigment
3-26-98 (B)	IND	Communication from Sepracor to FDA regarding initiation of Clinical Program
3-27-98	IND	Communication from Sepracor to FDA regarding white colorant information
4-2-98	IND	Communication from Sepracor to FDA regarding white Colorant information
4-3-98	IND	Teleconference between Sepracor and FDA regarding white pigments
4-13-98	IND	Submission: Faxed Container-Closures Data (1 volume)
5-6-98	IND	Submission: Protocol 003 & Final Investigator Brochure (1 volume)
6-22-98	IND	Communication from FDA to Sepracor providing comments from review of IND
9-18-98	IND	Protocol Amendment: Change in Protocol 091-003, New Investigators (1 volume)
9-28-98	IND	Response to FDA request for information; Information Amendment: Pharmacology- Toxicology (3 Genotoxicity reports, 1 volume)
12-8-98	IND	Submission: 2 Clinical reports (091-001, 091-002, 2 volumes)
3-11-99	IND	Submission: Initial IND safety report for Study 091-003 describing results of a teratology study in rabbits (preclinical embryo/fetal development)
5-20-99	IND	Submission: Annual Report covering the period from 26 March 1998 to 25 March 1999
7-23-99	IND	Information Amendment: Pharm/Tox Request for Review of Dose Selection Rationale for the Proposed 2-Year Inhalation Carcinogenicity Study in Rats (1 volume)
8-4-99	IND	Request by FDA for full audited draft report for the 28-Day Inhalation Toxicity Study in Rats
8-11-99	IND	Information Amendment: Pharm/Tox [new protocol for Study WIL-312050 (6-month inhalation study in rats) and final report for Study WIL-312021]
8-17-99	IND	Information Amendment: Pharm/Tox (final Tox and TK reports for Study WIL-312022, a 28-day inhalation study in dogs)

Date	Type	Activity
9-17-99	IND	Communication from FDA to Sepracor providing minutes of 9-7-99 Committee meeting with recommendations for the proposed rat study
12-13-99	IND	Protocol Amendment: New Protocol New Protocol 091-004 and updated Investigator's Brochure dated December 1999
12-14-99	IND	Information Amendment: CMC (Drug substance section includes information on establishment of absolute stereochemistry of the molecule and current method of manufacturing and controls processes. Drug product section provides CMC for two new doses: 0.096 mg/mL and 0.144 mg/mL.)
1-21-2000	IND	Communication from FDA to Sepracor providing comments regarding amendments dated September 28, 1998, and August 11 and 17, 1999 (serial numbers 005, 010, and 011), containing genetic and general toxicology reports of 4-week duration in rats and dogs, and a proposal for a 6-month inhalation toxicity study in rats
2-4-2000	IND	Information Amendment: Pharm/Tox (five pre-clinical reports: 090-460, 090-813, 090-464, 090-809, and 090-814)
2-15-2000	IND	Protocol Amendment: New Investigators (sixteen new investigators for Protocol 091-004)
3-9-2000	IND	Response to FDA Request for Information (preclinical information and data requested in FDA letter of January 21, 2000)
3-15-2000	IND	Protocol Amendment: Change in Protocol, New Investigator (Amendment 1 and Revised Protocol 1 for study 091-004 and nineteen new investigators for study 091-004)
4-14-2000	IND	Protocol Amendment: New Investigator (six investigators for Protocol 091-004)
5-19-2000	IND	Protocol Amendment: New Investigator (three new investigators for Protocol 091-004)
5-24-2000	IND	Submission: Annual Report for period of March 26, 1999, to March 31, 2000
6-6-2000	IND	Protocol Amendment: New Investigator - Revised 1572 Forms (10 sites)
6-7-2000	IND	Protocol Amendment: New Investigator
6-27-2000	IND	Protocol Amendment: New Investigator - Revised 1572 Forms for 091-004 (3 sites)
9-5-2000	IND	Protocol Amendment: New Investigator - Revised 1572 Forms (change in lab name from UCT International to ICON Laboratories for Protocol 091-004)
10-10-2000	IND	Protocol Amendment: New Protocol, New Investigator (Protocol 091-021)
11-6-2000 (A)	IND	Protocol Amendment: New Investigators Add 3 new PIs to Protocol 091-021
11-6-2000 (B)	IND	Protocol Amendment: New Investigator - Revised 1572 Forms for 3 PIs for Protocol 091-004
12-6-2000	IND	Protocol Amendment: New Investigator - Add 2 new PIs for Protocol 091-021, revised 1572 Form
2-1-2001	IND	Protocol Amendment: New Investigator for 091-021 and Information Amendment: Pharmacology/ Toxicology (10 preclinical reports and 1 amendment to a final report) (two volumes)
3-16-2001	IND	Protocol Amendment: New Investigator Information Amendment: Pharmacology/ Toxicology (Revised 1572s for Drs. Corren and Corser for Protocol 091-021, plus 11 new preclinical reports) (10 volumes)

Date	Type	Activity
5-4-2001	IND	Protocol Amendment: Change in Protocol (Amendment 2 for 091-021) and Information Amendment: Pharmacology/Toxicology (one protein binding report and five new bioanalytical reports)
5-10-2001	IND	Request by FDA for the list of Sepracor attendees for the 5-11-01 teleconference.
5-14-2001 (A)	IND	Faxed requested list of Sepracor attendees for May 11, 2001 teleconference.
5-14-2001 (B)	IND	Request by FDA for another teleconference for May 15 or 16, 2001, to discuss Protocol 091-021
5-15-2001	IND	Information Amendment: CMC (new formulations of 0.015 mg/mL, 0.030 mg/mL, and 0.060 mg/mL, each in 1 mL unit-dose vials)
5-16-2001	IND	Communication from Sepracor to FDA briefing documents for teleconference scheduled for May 16, 2001 for the discussion of Protocol 091-021
5-24-2001 (A)	IND	Communication from Sepracor to FDA regarding revised timeline for providing information requested during May 16, 2001, teleconference.
5-24-2001 (B)	IND	Communication from FDA to Sepracor confirming receipt of revised information timeline
5-24-2001 (C)	IND	Request by FDA for a teleconference on June 4, 2001, regarding a general discussion of adverse event reporting during clinical studies
5-25-2001 (A)	IND	General Correspondence: Requested List of Submissions. Protocol 190-001 – 190-004.
5-25-2001 (B)	IND	Communication from Sepracor to FDA regarding copy of Submission Serial No. 034 sent to Robert Meyer
6-1-2001	IND	Communication from Sepracor to FDA requesting information on the timing of teleconference to discuss Adverse Event Reporting would be held.
6-5-2001 (A)	IND	Request by FDA for attendees' names for teleconference held June 4, 2001, regarding safety reporting
6-5-2001 (B)	IND	Submission: Notice to Division that Serial No. 033 was inadvertently omitted from reporting sequence
6-5-2001 (C)	IND	Communication from Sepracor to FDA providing copy of cover letter and Form FDA 1571 for Serial No. 035
6-5-2001 (D)	IND	General Correspondence: Withdrawal of Protocol Amendment (Amendment 2 to Protocol 091-021 submitted May 4, 2001, in Serial No. 031)
6-6-2001 (A)	IND	Submission: IND Annual Report (April 1, 2000 through March 31, 2001)
6-6-2001 (B)	IND	Submission: Proposal for Juvenile Nonclinical Safety Assessment of (R,R)-Formoterol
6-12-2001	IND	Information Amendment: Pharmacology/Toxicology, Report #'s 090-818, 090-534, 090-536.
6-22-2001	IND	Communication from Sepracor to FDA regarding request for an EOP2 Meeting
6-28-2001	IND	Submission: Initial IND Safety Reports , 091-021 for subjects: JT/S023/R0054, SAT/S007/R0107, TCT/S021/R0113, LMK/S004/R0024

Date	Type	Activity
7-3-2001 (A)	IND	Communication from Sepracor to FDA faxing a copy of Serial No. 040
7-3-2001 (B)	IND	General Correspondence: End of Phase 2 Meeting Report
7-16-2001	IND	Information Amendment: Pharmacology/Toxicology, Report #'s 090-417, -418, -419, -452, & -475
7-17-2001	IND	FDA proposals for End of Phase II meeting
8-7-2001 (A)	IND	Fax from Sepracor to FDA forwarding the End of Phase II Meeting Information Package
8-7-2001 (B)	IND	Submission: End of Phase II Meeting Information Package
8-7-2001 (C)	IND	Communication between Sepracor and FDA regarding meeting for EOPII set for 9/6/2001
8-29-2001 (A)	IND	Communication from Sepracor to FDA informing the realignment of projects along Therapeutic Areas, and regarding the EOP II meeting
8-29-2001 (B)	IND	Protocol Amendment, New Protocol 091-010, and new investigator for 091-010
8-29-2001 (C)	IND	Communication from FDA to Sepracor regarding the time slot for CMC section of the EOPII meeting
8-29-2001 (D)	IND	Communication from FDA to Sepracor providing the list of attendees for September 6, 2001 EOP II Meeting
8-30-2001	IND	Communication from FDA to Sepracor finalizing EPO II meeting time and place
8-31-2001	IND	Communication from Sepracor to FDA regarding EOP II Meeting preparation
9-12-2001	IND	Submission: Revised Initial IND Safety Report for subject TCT/S021/R0113.
9-18-2001	IND	General Correspondence: Follow up to the End of Phase 2 meeting, EOP2 Draft Minutes, Request for a Teleconference.
9-20-2001	IND	Communication from Sepracor to FDA reporting on status of submissions
10-1-2001	IND	Information Amendment: Pharmacology/Toxicology
10-4-2001	IND	Communication from Sepracor to FDA regarding transfer of Regulatory Responsibility, Project Updates
10-10-2001	IND	Communication from Sepracor to FDA providing project update
10-11-2001	IND	General Correspondence: End of Phase 2 Meeting Minutes (CMC)
10-12-2001	IND	Project update
10-22-2001	IND	Protocol Amendment: Protocol 091-010 New Investigators, Revised Form FDA 1572
10-23-2001 (A)	IND	Submission: IND Safety Report: Initial Report (Subject TRW/S001), Initial Report (Subject LJO/S006)
10-23-2001 (B)	IND	Communication from Sepracor to FDA providing project update
10-25-2001	IND	Communication from Sepracor to FDA providing comments on Protocol 091-050



Date	Type	Activity
11-1-2001	IND	Communication from Sepracor to FDA regarding protocol 091-050 and 091-051 and the progress of each
11-2-2001	IND	Submission: Request for Special Protocol Assessment: Protocol 09-051
11-6-2001	IND	Communication from FDA to Sepracor requesting an additional copy of Serial No. 050
11-7-2001 (A)	IND	General Correspondence: Additional Copy of Serial No. 050
11-7-2001 (B)	IND	Communication from Sepracor to FDA regarding the additional copy of 091-051, the Division's Minutes from the EOP2 Meeting and the status of proposal for Juvenile Nonclinical Risk Assessment submitted on 6-6-01
11-20-2001	IND	Communication from Sepracor to FDA regarding minutes from EOP2 meeting held in September and feedback on proposal for Juvenile Nonclinical Risk Assessment
11-27-2001	IND	Communication from Sepracor to FDA regarding questions concerning Protocols 091-050 and 091-051
11-30-2001	IND	Communication from Sepracor to FDA regarding the submission of Protocol 091-050 on 11/7/01 in Serial No.051; the EOP2 Meeting Minutes; Clinical Studies for 091-003 and 091-004; and the 9-month dog study
12-3-2001	IND	FDA Request for Additional Copy of Serial No. 050
12-4-2001	IND	General Correspondence: Additional Copy of Serial No. 050
12-14-2001	IND	Communication between Sepracor and FDA regarding the status report for the special protocol assessment (091-051) and the 8 volume Nonclinical IND Information to be submitted
12-17-2001	IND	FDA acknowledgement of receipt of serial no. 050
12-18-2001	IND	Information Amendment: Pharmacology/Toxicology
12-19-2001	IND	Request by Sepracor for a status update on Special Protocol Assessment for study 091-051
12-20-2001 (A)	IND	Communication from FDA to Sepracor providing a letter containing FDA responses to questions regarding study 091-051
12-20-2001 (B)	IND	FDA responses to questions regarding study 091-051.
1-4-2002	IND	Information Amendment: Chemistry, Manufacturing, and Controls
1-14-2002	IND	Communication between Sepracor and FDA regarding the status report concerning the Division's minutes from the 9/6/01 EOP2 meeting.
2-7-2002	IND	Protocol Amendment: New Protocol, New Investigator (Protocol 091-050, V.1.2 dated 1-9-02, Amendment 2 dated 1-7-02, Amendment 1 dated 11-13-01)
2-15-2002	IND	Information Amendment: Pharmacology/ Toxicology (Sepr. Doc. Nos. 090-483, 090-489, 090-550, and 090-532)
2-27-2002	IND	Request by Sepracor for information regarding the date for receipt of the Division's minutes of the 9-6-01 EOP2 meeting
2-28-2002 (A)	IND	Protocol Amendment: New Investigators (21 investigators for 091-050)
2-28-2002 (B)	IND	Request by FDA for clarification on changes made to Protocol 091-050 (Serial No. 054); answer provided by Sepracor

Date	Type	Activity
3-15-2002	IND	Response to FDA Request for Information (Protocol 091-050 highlighted and with track changes)
3-28-2002	IND	Protocol Amendment: New Investigators (13) protocol 091-050
4-12-2002	IND	Protocol Amendment: New Protocol, New Investigator (091-051)
4-25-2002	IND	Information Amendment: Pharmacology/Toxicology
4-30-2002	IND	Protocol Amendment: New Investigators (8) Study 091-050
5-8-2002	IND	Submission: IND Safety Report: Initial Report (Subject BLA/S007/R0024) 091-050
5-13-2002	IND	Protocol Amendment: New Investigators (12) Study 091-051
5-16-2002	IND	Communication between Sepracor and FDA regarding the status of the Formoterol EOP II minutes from the September 6, 2001 meeting
5-21-2002	IND	Communication between Sepracor and FDA regarding the status of the Formoterol EOP II minutes from the September 6, 2001 meeting
5-22-2002	IND	Protocol Amendment: New Protocol, New Investigator (091-014) and New Protocol, New Investigator (091-015)
6-3-2002 (A)	IND	Protocol Amendment: New Investigators (091-014, 091-050 and 091-051)
6-3-2002 (B)	IND	Communication between Sepracor and FDA regarding Sepracor's request for a copy of the slides from the EOP-II CMC Meeting.
6-3-2002 (C)	IND	Communication between Sepracor and FDA regarding the EPOII Meeting Minutes from the Division
6-4-2002 (A)	IND	Communication from Sepracor to FDA regarding change in corporate address
6-4-2002 (B)	IND	Fax from FDA of the slides from the EOP-II CMC Meeting.
6-5-2002 (A)	IND	Protocol Amendment: New Protocol, New Investigator (091-060)
6-5-2002 (B)	IND	Adverse Event Report: IND Safety Report Initial: S009/R0061/DLH
6-18-2002 (A)	IND	Submission: IND Annual Report (April 1, 2001 through March 31, 2002)
6-18-2002 (B)	IND	Communication between Sepracor and FDA regarding the status of the EPOII Meeting Minutes
6-19-2002	IND	Request by FDA for an electronic copy of the slides presented at the EPOII Meeting
6-20-2002	IND	IND Safety Report: Initial Report (Subject BLA/S007/R0024)
6-25-2002	IND	Communication from FDA to Sepracor providing comments from FDA on Serial No. 064, dated May 22, 2002 Protocol NO. 091-014
7-1-2002 (A)	IND	Submission: IND Safety Report: Follow-up Report (Subject S007/R0024/BLA) 091-050

Date	Type	Activity
7-1-2002 (B)	IND	Communication between Sepracor and FDA regarding the CMC portion of the EOPII Meeting Minutes from the 9/6/01 meeting
7-3-2002	IND	FDA Official Minutes from September 6, 2001, EOPII CMC Meeting
7-8-2002	IND	Protocol Amendment: New Investigators
7-9-2002	IND	Submission: IND Safety Reports: Initial Report (Subject S008/R0840/RHS) Initial Report (Subject S014/R0869/JMW) Study 091-050
7-12-2002 (A)	IND	Submission: IND Safety Reports: Initial Report (S004/R0209/CAA) and Initial Report (S014/R0869/JMW) studies 091-050/091-020
7-12-2002 (B)	IND	Communication from Sepracor to FDA providing an electronic copy of Sepracor's Slides presented at the 9-6-01 EOP2 Meeting
7-19-2002	IND	Official FDA Minutes for EOPII (non-CMC) 9-6-01 Meeting
7-23-2002	IND	Submission: IND Safety Reports: Initial Reports: Subject Nos. S001/0818/HRS, S017/R0088/PEY, S034/R0868/MAH and Follow-up Reports: Subject Nos. S008/R0840/RHS and S014/R0869/JMW. Study # 190-050
7-26-2002	IND	Submission: IND Safety Reports: Initial Reports (S015/R0191/KDG and S047/R0225/LAT) and Follow-up Report (S034/R0868/MAH) study 091-050
7-31-2002	IND	Submission: IND Safety Reports: Initial Reports (Subject S008/R0205/PMS and S001/R5004/EMW) study 091-051
8-1-2002	IND	Protocol Amendment: Revised Protocol (091-014 and 091-015)
8-8-2002	IND	Protocol Amendment: New Investigators (3-050, 6-051 and 18-060)
8-9-2002	IND	Submission: IND Safety Reports: Initial Report (Subject S013/R0176/GAP) Follow-up Report (Subject S001/R5004/EMW) studies 091-050/091-051
8-12-2002	IND	Submission: IND Safety Reports: Initial Report (Subject S019/R0849/DMB and Initial Report (Subject S043/R0885/KMS) study 091-050
8-15-2002 (A)	IND	Request by FDA for Missing Page 2, Form FDA 1572 for Dr. V. Patel, from Serial No. 079, dated 8-9-2002.
8-15-2002 (B)	IND	General Correspondence: Response to Request for Information, Provide Missing Page 2, Form FDA 1572 for Dr. V. Patel
8-16-2002	IND	Submission: IND Safety Reports: Follow-up Report (Subject S001/R0818/HRS) and Follow-up Report (Subject S001/R5004/EMW) study 091-050/091-051
8-21-2002	IND	Submission: IND Safety Report: Follow Up Report (Subject S014/R0869/JMW)
8-27-2002	IND	Communication between Sepracor and FDA regarding the timeline for submission of a marketing application
9-3-2002	IND	Submission: IND Safety Report: Initial Report (Subject S007/R0919/SEY) study 091-050
9-10-2002	IND	Communication between Sepracor and FDA regarding Investigator Dr. W. Busse
9-11-2002	IND	Protocol Amendment: New Investigators (-050, -051, -060)
9-13-2002	IND	Protocol Amendment: New Protocol, New Investigator (091-013)
9-16-2002	IND	Submission: IND Safety Reports: Initial Report (Subject S014/R0923/DCR study -050) Follow up (Subject S007/R0919/SEY study -050) Follow up (Subject S008/R0205/PMS study -014)

Date	Type	Activity
9-17-2002	IND	Submission: IND Safety Report: Initial Report (Subject S007/R0051/PRC) study 091-050
9-20-2002	IND	Submission: IND Safety Reports: Initial Report (Subject S916/R2073/RAM) 091-060, Initial Report (Subject S018/R0122/HTH) 091-050, Initial Report (Subject S013/R0299/J-R) 091-050, Follow-up Report (Subject S013/R0176/GAP) 91-050 and Follow-up Report (Subject S009/R0061/DLH) 091-050
9-26-2002	IND	Submission: IND Safety Reports: Initial Reports (Subject S906/R2121/MWM) 3 initial reports on same subject for study 091-060
9-27-2002 (A)	IND	Information Amendment: Pharmacology / Toxicology
9-27-2002 (B)	IND	Submission: IND Safety Reports: Initial Report (Subject S028/R0905/ZAF) Initial Report (Subject S045/R0895/JEC) Follow-up (Subject S014/R0923/DCR) Follow-up (Subject S015/R0191/KDG) Study 091-050
10-1-2002	IND	Submission: IND Safety Reports: Follow-up Report (Subject S014/R0869/JMW 091-050) and Follow-up Report (Subject S018/R0122/HTH 091-050)
10-2-2002	IND	Telephone discussion between Sepracor and FDA regarding FDA's comments on protocol 091-013 submitted on 9/19
10-7-2002	IND	Submission: IND Safety Report: Follow-up Report (Subject S034/R0868/MAH) 091-050
10-9-2002	IND	Protocol Amendment: New Investigators (-015, -050, -051, -060) Revised 1572's (-014, -015, -050, -051)
10-11-2002	IND	Submission: IND Safety Reports: Follow Up Reports (Subject S043/R0885/KMS [091-050], Subject S028/R0905/ZAF [091-050], Subject S906/R2121/MWM [091-060], Subject S916/R2073/RAM [091-060])
10-15-2002	IND	Submission: IND Safety Reports: Follow Up Reports (Subject S007/R0051/PRC [091-050], Subject S045/R0895/JEC [091-050], Subject S906/R2121/MWM [091-060])
10-16-2002	IND	Communication from FDA to Sepracor providing preliminary Clinical Pharmacology comments on protocol 091-013
10-24-2002	IND	Submission: IND Safety Report: Follow Up Report (Subject S034/R0868/MAH [091-050])
10-31-2002	IND	Submission: IND Safety Report: Follow Up Report (Subject S015/R0191/KDG [091-050])
11-1-2002	IND	Submission: IND Safety Report: Follow up report (Subject S007/R0919/SEY) study 091-050
11-5-2002 (A)	IND	Protocol Amendment: New Protocol, New Investigator [091-012]
11-5-2002 (B)	IND	Submission: IND Safety Report: Follow Up Report (Subject S013/R0299/J-R [091-050])
11-7-2002	IND	Submission: IND Safety Report: Initial Reports (Subject S0905/R2125/QBM [091-060], Subject S506/R2020/GPS [091-060], Subject S001/R5086/BJN [091-051], Subject S015/R0925/DAR [091-050], Follow Up Report (Subject S047/R0225/LAT [091-050])
11-8-2002	IND	Information Amendment: CMC
11-11-2002 (A)	IND	Protocol Amendment: New Investigators (3) 091-051, (9) 091-060
11-11-2002 (B)	IND	Information Amendment: CMC Protocol Amendment: New Protocol, New Investigator (091-016)

Date	Type	Activity
11-11-2002 (C)	IND	Submission: IND Safety Reports: 2 Initial Reports for Study 091-051 (Subject S010/R5151/FAE, Subject S007/R5810/J-W)
11-11-2002 (D)	IND	Communication from Sepracor to FDA providing a fax copy of IND Initial Safety Report (7-Day)
11-12-2002	IND	Submission: Hard copy of IND Safety Report: 7-Day Fax Transmission (Subject S020/R5089/DLO)
11-14-2002 (A)	IND	Submission: IND Safety Report: Initial Report (Subject S014/R0923/DCR) Follow-up Report (Subject S007/R5810/J-W) study 091-050/091-051
11-14-2002 (B)	IND	Communication from FDA to Sepracor providing Confidentiality Certificate protecting the identity of research subjects involved in clinical studies under IND 55,302
11-15-2002	IND	Submission: IND Safety Reports: Initial Report (Subject S012/R5093/CJW [091-051]) and Follow Up Report (Subject S013/R0299/J-R [091-050])
11-26-2002	IND	Submission: IND Safety Reports: Initial Report (Subject S005/R5114/WCG) Follow-up Report (Subject S012/R5093/CJW)
11-27-2002 (A)	IND	Communication from Sepracor to FDA providing a fax copy of IND Safety Report Initial Report (7 day fax transmission) Follow-up Report (7 day fax transmission)
11-27-2002 (B)	IND	Submission: Hard copy of IND Safety Reports faxed on this date. (Subject S025/R5177/NGB, Subject S007/R5810/J-W)
12-2-2002 (A)	IND	Submission: IND Safety Reports: Study 091-050 Initial & Follow-up (S004/R0399/WAD, S018/R0122/HTH), Study 091-051 - 1 Initial, 2 follow-up (S007/R5154/JKH, S010/R5151/FAE, S020/R5089/DLO)
12-2-2002 (B)	IND	Information Amendment: CMC
12-6-2002 (A)	IND	Protocol Amendment: New Investigators (7) 1-016, 1-051, 5-060
12-6-2002 (B)	IND	Submission: IND Safety Report: Follow-up Report: Subject S025/R5177/NGB, study 091-051
12-6-2002 (C)	IND	IND Safety Report: 7-Day Fax Transmission, study 091-051
12-9-2002	IND	Submission: Hard copy of IND Safety Report: 7-Day Fax Transmission, study 091-051 originally sent on 12/6/2002
12-10-2002	IND	Submission: IND Safety Reports: Initial Report (Subject S004/R5125/DLB [091-051]), Follow Up Report (Subject S017/R0088/PEY [091-050])
12-12-2002	IND	Telephone discussion between Sepracor and FDA regarding Clinical Pharmacology questions on study 091-016
12-13-2002	IND	Submission: IND Safety Report: Initial Report (Subject S015/R0942/JMB [091-050])
12-16-2002	IND	Submission: IND Safety Reports: Follow up Report (Subject S004/R0399/WAD study -050) Follow up Report (Subject S005/R5114/WCG study -051)
12-17-2002	IND	Submission: IND Safety Reports: Initial Report (Subject 903/R2123/LJM study 091-060) Initial Report (Subject S919/R20075/H-S study 091-060) Follow up Report (Subject S906/R2121/MWM study 091-060)

Date	Type	Activity
12-20-2002 (A)	IND	Protocol Amendment: Revised Protocols -050, -051 and -060
12-20-2002 (B)	IND	Submission: IND Safety Reports: 3 Initial and 6 Follow-up Subject S010/R0317/FMF, Subject S906/R2121/MWM, Subject S009/R0140/DLS, Subject S906/R2121/MWM, Subject S009/R0240/DLS, Subject S919/R2075/H-S, Subject S018/R0122/HTH, Subject S004/R5125/DLB, Subject S002/R5073/EHW
12-23-2002	IND	Submission: IND Safety Report: Follow Up Report (Subject S903/R2123/LJM [091-060])
1-2-2003 (A)	IND	Submission: IND Safety Report: Initial Report (Subject S502/R2189/KMC [091-060]), (2) Follow Up Report (Subject S015/R0942/JMB [091-050])
1-2-2003 (B)	IND	Communication from FDA to Sepracor regarding comments on the 091-016 protocol from the biopharmaceutics reviewer
1-2-2003 (C)	IND	Communication from FDA to Sepracor providing comments pertaining to Protocol 091-016
1-3-2003	IND	Submission: IND Safety Reports: Follow Up Report (Subject S010/R0317/FMF [-050]), Follow Up Report (Subject S906/R2121/MWM [-060]), Follow Up Report (Subject S005/R5114/WCG [-051])
1-6-2003	IND	Submission: IND Safety Reports: Initial Report (Subject S503/R220/ERB [091-060]), Initial Report (Subject S005/R5114/WCG [091-051])
1-8-2003	IND	Protocol Amendment: New Investigators (091-051 [1], 091-060 [2])
1-10-2003	IND	Submission: IND Safety Reports: Initial Report (Subject S013/R0385/BAP, Initial Report (Subject S022/R0349/NSD, Initial Report (Subject S059/R0438/TRW) [-050]; Initial Report (Subject S919/R2075/H-S), Initial Report (Subject S503/R2240/RGB) [-060]; Follow Up Report (Subject S010/R5151/FAE) [-051]
1-13-2003	IND	Submission: IND Safety Reports 2 Initial Reports (Subject S012/R5242/PJS and Subject S501/R2139/LWP) studies -051 and -060
1-15-2003	IND	Submission: IND Safety Reports 1 Initial Report (Subject S919/R2075/H-S) 2 Follow up Reports (Subject S919/R2075/H-S) (Subject S059/R0438/TRW) studies -050 and -060
1-17-2003	IND	Submission: IND Safety Report 1 Follow-up Report (Subject S009/R0240/DLS) study-050
1-21-2003 (A)	IND	Submission: IND Safety Reports: 4 Follow-up Reports for the same subject (S906/R121/MWM)
1-21-2003 (B)	IND	Submission: IND Safety Report: Follow-up report (Subject S0502/R2189/KMC)
1-22-2003 (A)	IND	Submission: IND Safety Reports: 2 initial/1 follow-up Studies -050 and -060 (Subjects S904/R2217/JLL, S049/R0428/L-F, S013/R0385/BAP)
1-22-2003 (B)	IND	Submission: IND Safety Report: Follow-up Report (Subject S014/R0923/DCR) study -050
1-23-2003	IND	Submission: IND Safety Reports: 3 Initial Reports studies -050 and -060 (Subject S047/R0397/BJD, S503/R2200/ERB, S525/R2104/EFA)
1-24-2003	IND	Submission: IND Safety Report: Follow-up Report (Subject S004/R0399/WAD) study 091-050
1-28-2003	IND	Submission: IND Safety Reports: 3 Initial, 2 Follow-up (Subjects S042/R0410/JEF, S512/R2245/CHL, S502/R2189/KMC, S022/R0349/NSD, S503/R2240/RGB) Studies -050 and -060

Date	Type	Activity
1-29-2003	IND	Submission: IND Safety Report: 3 Follow-up reports (Subject S007/R5810/J-W, Subject S002/R5073/EHW, Subject S025/R5177/NGB [091-051])
2-3-2003	IND	Submission: Initial IND Safety Report: (7-Day Fax Transmission) Study 091-060, (Subject No. S503/R2009/MHK)
2-4-2003	IND	Submission: IND Safety Reports: Copy of 7-Day Fax Transmission (Subject S503/R2009/MHK [091-060]), Follow up Report (Subject S015/R0925/DAR [091-050])
2-6-2003	IND	Submission: IND Safety Reports: 1 Initial (Subject S026/R5229/SEP) 3 Follow-up (Subject S025/R5177/NGB, S018/R0122/HTH, S503/R2200/ERB) Studies -050, -051, -060
2-7-2003	IND	Submission: IND Safety Reports: 1 Initial (Subject S028/R0419/HGS) 7 Follow-up (Subjects S047/R0397/BJD, S022/R0349/NSD, S001/R5086/BJN, S905/R2125/QBM, S004/R0399/WAD and 2 for S919/R2075/H-S) studies -050, -051 and -060
2-10-2003 (A)	IND	Protocol Amendment: Revised Protocol (091-016)
2-10-2003 (B)	IND	Protocol Amendment: New Investigators (091-060)
2-11-2003	IND	Submission: IND Safety Report: Follow-up Report (Subject S026/R5229/SEP) study 091-051
2-13-2003	IND	Submission: IND Safety Reports: Initial Report (Subject S502/R2004/RDH [091-060]), Follow up Report (Subject S503/R2200/ERB [091-060])
2-14-2003	IND	Submission: IND Information Amendment: Pharmacology / Toxicology. 7 nonclinical studies
2-20-2003	IND	Submission: IND Safety Reports: Follow Up Report (Subject S509/R0438/TRW [-050]), Follow Up Report (Subject S007/R5810/J-W [-051])
2-21-2003	IND	Submission: IND Safety Report: Follow-up Report: (Subject S508/R2009/MHK) study -060
2-28-2003 (A)	IND	Communication from Sepracor to FDA providing IND Safety Report (7-Day Fax Transmission) Subject No. S010/R0317/FMF study 091-050
2-28-2003 (B)	IND	Submission: IND Safety Reports: 6 Initial, 2 Follow-up (Subject No. S007/R0950/RAL [2 initial reports])(Subject No. S065/R0436/EAM) (Subject No. S049/R0428/L-F) (Subject No. S902/R2273/JCK) (Subject No. S501/R2028/RDW) (Subject No. S502/R2189/KMC) (Subject No. S010/R0317/FMF) Studies -050 and -060
2-28-2003 (C)	IND	Communication from Sepracor to FDA regarding assignment changes in regulatory directors at Sepracor
3-4-2003	IND	Submission: IND Safety Reports: Follow Up Report (Subject S503/R2009/MHK), Follow Up Report (Subject S501/R2028/RDW) study 091-060
3-7-2003	IND	Protocol Amendment: New Investigators (091-051, 091-060)
3-10-2003	IND	Submission: IND Safety Report: Follow-up report (Subject S026/R5529/SEP) study 091-051
3-12-2003	IND	Submission: IND Safety Reports: Initial Report (Subject S510/R2050/ADC) Initial Report (Subject S063/R0968/MAO) Follow-up Report (Subject S049/R0428/L-F) Studies -050 and -060
3-17-2003	IND	Telephone discussion between Sepracor and FDA regarding SAE Reporting Schedules
3-18-2003	IND	Protocol Amendment: Revised Protocol (091-012)
3-20-2003	IND	Submission: IND Safety Reports: 1 initial (Subject S024/R0970/MJW) and 1 follow-up (Subject S010/R0317/FMF) study -050

Date	Type	Activity
3-21-2003	IND	Submission: IND Safety Reports: 1 Initial Report (Subject S001/R5299/WCM [-051]), 3 Follow Up Reports (Subject S025/R5177/NGB [-051]), (Subject S007/R0950/RAL [-050]), (Subject S902/R2273/JCK [-060])
3-24-2003	IND	Submission: IND Safety Reports: Follow Up Report (Subject S028/R0419/HGS [091-050]), Follow Up Report (Subject S024/R0970/MJW [091-050])
3-31-2003	IND	Telephone discussion between Sepracor and FDA regarding the Unblinded SAEs from the Program Safety Evaluation
4-1-2003 (A)	IND	Submission: IND Safety Reports: Initial Report (Subject S504/R2281/DHK [-060]) Follow Up Report (Subject S501/R2028/RDW [-060]), Follow Up Report (Subject S510/R2050/ADC [-060]), Follow Up Report (Subject S026/R5229/SEP [-051])
4-1-2003 (B)	IND	Protocol Amendment: New Investigators (091-051, 091-060)
4-2-2003	IND	Submission: IND Safety Report: Initial Report (Subject S902/R2273/JCK [091-060])
4-9-2003	IND	Submission: IND Safety Reports: Initial Report (Subject S027/R0952/BLJ [091-050]), Follow Up Report (Subject S010/R0317/FMF [091-050])
4-15-2003	IND	Submission: IND Safety Reports: Follow Up Report (Subject S024/R0970/MJW [091-050]). Follow Up Report (Subject S063/R0968/MAO [091-050])
4-16-2003	IND	Submission: IND Safety Report: Follow Up Report (Subject S065/R0436/EAM [091-050]), Correction to a Follow Up Report (Serial No. 164)
4-18-2003	IND	Submission: IND Safety Report: Follow up report (Subject S014/R0923/DCR) study 091-050
4-22-2003	IND	Submission: IND Safety Reports: Initial Report (Subject S001/R0474/JDO [091-050]), Initial Report (Subject S502/R2341/REH [091-060])
4-23-2003	IND	Submission: IND Safety Report: Follow Up Report (Subject S504/R2281/DHK [091-060])
4-24-2003	IND	General Correspondence: Safety Surveillance System
4-25-2003	IND	Submission: IND Safety Report: Follow Up Report (Subject S029/R5295/TMM)
4-30-2003	IND	Submission: IND Safety Report: 7-Day Fax Transmission (Subject S017/R5283/ERR [091-051])
5-1-2003 (A)	IND	Protocol Amendment: New Investigators (091-014, 091-051, 091-060)
5-1-2003 (B)	IND	Submission: IND Safety Report: Follow Up Report (Subject S001/R0474/JDO [091-050])
5-2-2003	IND	Submission: IND Safety Report: Follow Up Report (Subject S502/R2341/REH [091-060])
5-9-2003	IND	Submission: IND Safety Reports: Initial Report (Subject S015/R0501/EFT [091-050]), Follow Up Report (Subject S027/R0952/BLJ [091-050])
5-13-2003 (A)	IND	Submission: IND Information Amendment: Pharmacology / Toxicology. 4 nonclinical studies
5-13-2003 (B)	IND	Submission: IND Safety Reports: Follow Up Report (Subject S501/R2028/RDW [091-060]), Follow Up Report (Subject S027/R0952/BLJ [091-050])



Date	Type	Activity
5-15-2003	IND	Communication from Sepracor to FDA providing follow-up IND Safety Report subject (S017/R5283/ERR) study 091-051
5-16-2003 (A)	IND	Submission: IND Safety Reports: Follow-up Reports 7-Day fax transmission – follow-up IND Safety Report subject (S017/R5283/ERR) study 091-051 and Follow-up Report Subject (S015/R0501/EFT) study 091-050
5-16-2003 (B)	IND	Submission: IND Safety Report: Initial Report (Subject S512/R2145/MDM [091-060])
5-19-2003	IND	Submission: IND Safety Report: Follow Up Report (Subject S010/R5151/FAE [091-051])
5-20-2003 (A)	IND	Communication from Sepracor to FDA providing initial IND Safety Report (7-day Fax Transmission) study 091-051, subject (S023/R5321/EAW)
5-20-2003 (B)	IND	Submission: IND Safety Reports: Initial Report (7-day Fax Transmission) study 091-051, subject (S023/R5321/EAW) and Follow-up report study 091-051, Subject (S029/R5295/TMM)
5-22-2003	IND	Submission: IND Safety Reports: Follow Up Report (Subject S007/R0950/RAL [091-050]), Follow Up Report (Subject S001/R5299/WCM [091-051])
5-27-2003	IND	Submission: IND Safety Report: Initial Report (Subject S901/R2072/H-J [091-060]), Follow Up Report (Subject S001/R0474/JDO [091-050])
6-4-2003	IND	Submission: IND Annual Report (April 1, 2002 through March 31, 2003)
6-5-2003 (A)	IND	Protocol Amendment: New Investigators (091-051, 091-060)
6-5-2003 (B)	IND	Telephone discussion between Sepracor and FDA regarding Serial No. 169 which provided information on the approach to the Safety Surveillance utilized in the clinical development process
6-10-2003	IND	Submission: IND Safety Reports: Initial Report (Subject S537/R2319/JCC) Follow-up Report (Subject S001/R5004/EMW) Follow-up Report (Subject S001/R0474/JDO) studies –050, -051 and -060
6-11-2003	IND	Submission: IND Safety Report: Follow-up report (Subject S022/R0349/NSD) study 091-050
6-13-2003	IND	Submission: IND Safety Reports: Initial Report (Subject S002/R5868/DLH) Follow-up Report (Subject S012/R5242/PJS) both are from study 091-051
6-17-2003	IND	Submission: IND Safety Reports: Initial Report (Subject S019/R5344/MVR [091-051])
6-18-2003	IND	Submission: IND Safety Report: Initial Report (Subject S026/R5385/JRW [091-051])
6-19-2003	IND	Telephone discussion between Sepracor and FDA regarding FDA's comments on the safety surveillance submitted in Serial No. 169
6-23-2003	IND	Submission: IND Safety Reports: Initial Report (Subject S066/R0974/BGT [091-050]), Follow Up Report (Subject S504/R2281/DHK [091-060])
6-25-2003	IND	Submission: IND Safety Reports: Initial Reports (S006/R5357/BJC [-051], S502/R2257/RDE [-060], S019/R0523/P-K [-050])
6-26-2003 (A)	IND	Protocol Amendment: New Investigators: 091-016, 091-051, 091-060
6-26-2003 (B)	IND	Submission: IND Safety Report: Follow-up Report (Subject S537/R2319/JCC [091-060])

Date	Type	Activity
6-26-2003 (C)	IND	Telephone discussion between Sepracor and FDA regarding Safety Surveillance Comments
7-1-2003	IND	Submission: IND Safety Reports: Follow up Report (Subject S008/R0205/RMS) study -014 and Initial Report (Subject S509/R2186/GSB) study -060
7-3-2003	IND	Submission: IND Safety Reports: Follow up Report (Subject S017/R5283/ERR) study 091-051, Initial Report (Subject S501/R2246/JFG) study 091-060
7-8-2003	IND	Submission: IND Safety Reports: 1 Initial Report (S014/R0975/CLC) study 091-050 2 Follow up Reports: (S002/R5868/DLH) (S019/R5344/MVR) study 091-051 1 Follow-up Report (S901/R2072/H-J) study 091-060
7-17-2003 (A)	IND	Communication from Sepracor to FDA providing IND Safety Report: Initial Report: (7-Day Fax Transmission) subject S026/R5229/SEP study 091-051
7-17-2003 (B)	IND	Submission: IND Safety Reports: 7-Day Fax Transmission: Subject S026/R5229/SEP study 091-051, Follow up Report: Subject S026/R5229/SEP study 091-051, Follow-up Report Subject S014/R095/CLC study 091-050
7-18-2003	IND	Submission: IND Safety Report: Follow up Report Subject (S002/R5868/DLH) Study 091-051
7-23-2003 (A)	IND	Communication from Sepracor to FDA providing IND Safety Report: Initial Report: 7-Day Fax Transmission (Subject S907/R2088/CWH) study 091-060
7-23-2003 (B)	IND	Submission: IND Safety Report: Initial Report: (Subject S905/R2348/BMJ), Initial Report: (7-Day Fax: Subject S907/R2088/CWH) study 091-060
7-28-2003 (A)	IND	Telephone discussion between Sepracor and FDA regarding the status of the letter from FDA concerning comments on Safety Surveillance
7-28-2003 (B)	IND	Information Amendment: Chemistry, Manufacturing, and Controls
7-29-2003	IND	Submission: IND Safety Report: Initial Report (Subject S931/R2585/JRL) Follow Up Report (Subject S502/R2257/RDE), Follow Up Report (Subject S501/R2246/JFG) study 091-060
7-30-2003 (A)	IND	Submission: IND Safety Report: Initial Report (Subject S007/R5418/RAH [091-051]), Initial Report (Subject S501/R2520/L-B [091-060])
7-30-2003 (B)	IND	General Correspondence: USAN Name (Change from (R,R)-Formoterol L-tartrate to Arformoterol tartrate)
7-31-2003 (A)	IND	Communication from Sepracor to FDA providing IND Safety Report: Follow Up: 7-Day-Fax Transmission (Subject S007/R5418/RAH) study 091-051
7-31-2003 (B)	IND	Submission: IND Safety Report: Follow Up Report: (7-Day Fax: Subject S007/R5418/RAH), Follow Up Report: (Subject S004/R5125/DLB), study 091-051
8-1-2003	IND	Submission: IND Safety Reports: Follow-up Report (Subject S066/R0974/BGT) study 091-050 Follow-up Report (Subject S002/R5868/DLH) Study 091-051
8-5-2003	IND	Protocol Amendment: New Investigators (091-051 and 091-060)
8-6-2003	IND	Submission: IND Safety Report: Follow Up Report (Subject S905/R2348/BJM [091-060])
8-7-2003	IND	Submission: IND Safety Report: Initial Report (Subject S001/R5334/PSJ [091-051])

Date	Type	Activity
8-11-2003	IND	Submission: IND Safety Reports: Initial Report (Subject S522/R2065/A-S [-060]), Follow Up Reports: (Subject S931/R2585/JRL [-060]), (Subject S907/R2088/CWH [-060]), (Subject S049/R0428/L-F [091-050])
8-18-2003	IND	General Correspondence: Open Label Comparator Adverse Event (Subject S507/R2368/WMF) 091-060
8-19-2003 (A)	IND	Submission: IND Safety Reports: Follow Up Reports (Subject S905/R2348/BMJ [-060]), Subject (S509/R2186/GSB [-060])
8-19-2003 (B)	IND	FDA response to Submission of 4/24/03, Serial No. 169, General Correspondence: Safety Surveillance System
8-19-2003 (C)	IND	Fax from FDA of the Response to Submission of 4/24/03, Serial No. 169, General Correspondence: Safety Surveillance System
8-21-2003	IND	Protocol Amendment: Revised 1572's (Protocols 091-013, 091-014, 091-015, 091-016, 091-051, 091-060)
8-25-2003	IND	Submission: IND Safety Report: Follow Up Report (Subject S001/R5334/PSJ [091-051])
8-28-2003 (A)	IND	Submission: IND Safety Report: Initial Report (Subject S909/R2214/CWM) study 091-060
8-28-2003 (B)	IND	Information Amendment: Revised Investigator's Brochure
9-2-2003	IND	Submission: IND Safety Report: Follow Up Report (Subject S007/R5418/RAH [091-051])
9-4-2003 (A)	IND	Communication from Sepracor to FDA providing IND Safety Report: Initial Report: 7-Day Fax Transmission (Subject S037/R5466/R-L [091-051])
9-4-2003 (B)	IND	Submission: IND Safety Report: Initial Report (7-Day Fax: Subject S037/R5466/R-L [091-051])
9-8-2003	IND	IND Safety Report: Initial Report (Subject S502/R2341/REH [091-060])
9-9-2003 (A)	IND	Protocol Amendment: Revised Protocol (091-015)
9-9-2003 (B)	IND	Submission: IND Safety Reports: Follow Up Report (Subject S931/R2585/JRL [-060]), Follow Up Report (Subject S019/R0523/P-K [-050])
9-10-2003	IND	Submission: IND Safety Report: Initial Report (Subject S507/R2525/M-B [091-060])
9-11-2003	IND	Submission: IND Safety Report: Initial Report (Subject S906/R2513/OBG [091-060])
9-12-2003	IND	Submission: IND Safety Reports: Initial Report (Subject S501/R2282/PAD [091-060]), Initial Report (Subject S904/R2251/CJT [091-060])
9-17-2003 (A)	IND	Submission: IND Safety Reports: Follow Up Report (Subject S909/R2214/CWM [091-060])
9-17-2003 (B)	IND	Protocol Amendment: New Protocol (091-026), New Investigators. (-026, -051) Revised Protocols. (-060)
9-18-2003	IND	Submission: IND Safety Reports: Initial Report (MFR 2003SP000002 [-060]), Initial Report (MFR 2003SP000001 [-051])
9-19-2003	IND	Submission: IND Safety Reports: Initial Report (MFR 2003SP000003 [-051]), Initial Report (MFR 2003SP000004 [-060])

Date	Type	Activity
9-23-2003 (A)	IND	Submission: IND Safety Reports: Initial Report (MFR 2003SP000005 [-060])
9-23-2003 (B)	IND	Information Amendment: Pharmacology/Toxicology
9-25-2003	IND	Submission: IND Safety Reports: Follow Up Report (Subject S502/R2341/REH [-060])
9-30-2003	IND	Submission: IND Safety Reports: Follow-up Reports: (MFR 2003SP000002) and (MFR 2003SP000001) studies 091-051 and 091-060
10-1-2003 (A)	IND	Communication from Sepracor to FDA providing IND Safety Report: 7-Day Fax Transmission (MFR 2003SP000004) study 091-060
10-1-2003 (B)	IND	Submission: IND Safety Report: Follow-up Report s (7-Day Fax Transmission) (MFR 2003SP000004) study 091-060 and (MFR 2003SP000003) study 091-051
10-2-2003	IND	Submission: IND Safety Reports: Follow Up Reports: (Subject S501/R2282/PAD [-060]), (Subject S065/R0436/EAM, Subject S007/R0950/RAL, Subject S018/R0122/HTH [-050])
10-3-2003	IND	Submission: IND Safety Reports: Initial Report (MFR 2003SP000008 [-060]), Follow Up Report (MFR 2003SP000005 [-060])
10-6-2003 (A)	IND	Information Amendment: CMC
10-6-2003 (B)	IND	Protocol Amendment: Revised Protocol Version 2.0 091-051
10-7-2003	IND	Submission: IND Safety Report: Initial Report (MFR 2003SP000010 [-060])
10-9-2003	IND	Submission: IND Safety Report: Follow Up Report (Subject S037/R5466/R-L [091-051])
10-10-2003 (A)	IND	Submission: ND Safety Report: Follow Up Report (MFR 2003SP000003-fu2 [091-051])
10-10-2003 (B)	IND	General Correspondence: Safety Surveillance System
10-14-2003	IND	Submission: IND Safety Report: Follow Up Report (MFR 2003SP000004-fu2 [091-060])
10-16-2003 (A)	IND	Submission: IND Safety Report: Follow Up Report (Subject S907/R2088/CWH [091-060])
10-16-2003 (B)	IND	Protocol Amendment: New Investigators (091-026)
10-23-2003	IND	Submission: IND Safety Reports: Initial Report (MFR 2003SP000013 [091-051]), Initial Report (MFR 2003SP000014 [091-060])
10-24-2003	IND	Submission: IND Safety Report: Follow Up Report (Subject S906/R2513/OBG [091-060])
10-27-2003	IND	Submission: IND Safety Report: Initial Report: MFR. No. 2003SP000016 study 091-060
10-31-2003	IND	Submission: IND Safety Reports: Initial Report (MFR 2003SP000022 [091-060]), Initial Report (MFR 2003SP000024 [091-051])
11-3-2003	IND	Submission: IND Safety Report: Follow Up Report (MFR 2003SP000008 [091-060])
11-7-2003	IND	Submission: IND Safety Reports: Follow Up Reports to Unblinding (091-050)
11-12-2003 (A)	IND	Protocol Amendment: New Investigators (091-026)

Date	Type	Activity
11-12-2003 (B)	IND	Submission: IND Safety Reports: Follow Up Reports (MFR 2003SP000010-FU1, 2003SP000022-FU1 [091-060]), Follow Up Report (MFR 2003SP000024-FU1 [091-051])
11-17-2003	IND	Submission: IND Safety Reports: Initial Reports (MFR 2003SP000032, 2003SP000037 [091-060])
11-18-2003	IND	General Correspondence: Request for Type C Meeting
11-19-2003	IND	Submission: IND Safety Reports: Initial Reports (MFR 2003SP000031, 2003SP000034 [091-060])
11-21-2003	IND	Submission: IND Safety Reports: Initial Reports (MFR 2003SP000035 [091-060])
11-25-2003	IND	Submission: IND Safety Reports: Initial Reports (MFR 2003SP000036 [-051], MFR 2003SP000040 [-051], MFR 2003SP000041 [-060], MFR 2003SP000045 [-060]), Follow Up Report (MFR 2003SP000031 [-060])
12-2-2003	IND	Request by Sepracor for Type C Meeting –Follow-up
12-3-2003 (A)	IND	Submission: IND Safety Report: Initial Report (MFR 2003SP000046 [-051])
12-3-2003 (B)	IND	Communication from FDA to Sepracor regarding the scheduling of the Type C Meeting
12-5-2003	IND	Submission: IND Safety Reports: Initial Reports (MFR 2003SP000051, 2003SP000052 [091-060])
12-9-2003	IND	Submission: IND Safety Report: Initial Report (MFR 2003SP000053 [091-051])
12-10-2003 (A)	IND	Communication from Sepracor to FDA providing Type C Meeting- Draft Questions
12-10-2003 (B)	IND	General Correspondence: Draft Questions for the Type C Meeting
12-12-2003	IND	Protocol Amendment: New Investigators 091-026
12-15-2003	IND	Submission: IND Safety Reports: Follow Up Report (Subject S904/R2251/CJT [091-060])
12-16-2003	IND	Submission: IND Safety Report: Follow Up Report (MFR 2003SP000002 [091-060])
12-17-2003	IND	Submission: IND Safety Report: Initial Report (MFR 2003SP000055 [091-060]), Follow Up Report (MFR 2003SP000052-FU1 [091-060], MFR 2003SP000040-FU1 [091-051])
12-19-2003	IND	Submission: IND Safety Reports: Initial Report (MFR 2003SP000057[091-051]), Initial Report (MFR 2003SP000059[091-051]), Follow Up Report (MFR 2003SP000053 [091-051]), Follow Up Report (MFR 2003SP000045 [091-060]), Follow Up Report (MFR 2003SP000041 [091-060])
12-22-2003	IND	Submission: IND Safety Reports: Follow Up Report (S037/R5466/R-L [091-051])
12-23-2003 (A)	IND	Submission: Response to FDA Request for Information: Safety Surveillance System
12-23-2003 (B)	IND	Submission: IND Safety Reports: Initial Report (MFR 2003SP000062 [091-026], Follow Up Report (Subject S906/R2513/OBG [091-060])
1-6-2004	IND	Communication between Sepracor and FDA regarding Type C Meeting Package, the location of the Meeting, and the submission of Responses to FDA Request for Information
1-9-2004	IND	Communication from Sepracor to FDA regarding Type C Meeting Package

Date	Type	Activity
1-12-2004 (A)	IND	Submission: IND Safety Report: Initial Report (MFR 2003SP000065 [091-060])
1-12-2004 (B)	IND	Follow-up communication regarding Type C meeting package
1-14-2004 (A)	IND	Communication from Sepracor to FDA providing IND Safety Report: Initial Report - 7-Day Fax Transmittal (MFR. 2004SP000006)
1-14-2004 (B)	IND	Submission: IND Safety Report: 7-Day (MFR. 2004SP000006)
1-14-2004 (C)	IND	General Correspondence: Type C Meeting Information Package
1-19-2004 (A)	IND	Submission: IND Safety Reports: Initial Reports (MFR 2004SP000001, 2004SP000004 [091-060]), Initial Report (MFR 2004SP000006 [091-051])
1-19-2004 (B)	IND	Submission: IND Safety Reports: Initial Reports (MFR 2004SP000002, 2004SP000005), Follow-Up Report (MFR 2003SP000062 [091-026])
1-20-2004	IND	Protocol Amendment: Amendment 2, Revised Protocol, New Investigators, Revised 1572's for protocol 091-026
1-22-2004	IND	Submission: IND Safety Reports: Initial Reports (MFR 2004SP000009, 2004SP000011 [091-060])
1-23-2004	IND	Communication from FDA to Sepracor providing list of attendees for the February 9, 2004 meeting between Sepracor and FDA
1-26-2004	IND	Information Amendment: Pharmacology/Toxicology (090-836)
1-27-2004	IND	Submission: IND Safety Reports: Initial Report (MFR 2004SP000013 [091-060]), Initial Report (MFR 2004SP000015 [091-051])
1-29-2004	IND	Follow-up communication regarding the list of attendees from FDA for the Type C Guidance Meeting on February 9, 2004
1-30-2004	IND	Submission: IND Safety Reports: Initial Report (MFR 2004SP000016 [091-060]), Initial Report (MFR 2004SP000017 [091-026]), Follow-Up Report (MFR 2004SP000005-FU1[091-026])
2-3-2004 (A)	IND	FDA Pharm/Tox Reviewer Request for Information regarding the amount of desformoterol that will typically be in the drug substance and drug product referred to in study 090-836 (Serial No. 277)
2-3-2004 (B)	IND	Response to FDA Pharm/Tox Reviewer's Earlier Request for Information
2-5-2004	IND	Submission: IND Safety Reports: Initial Report (MFR 2004SP000020 [091-060]), Follow-Up Report (MFR 2003SP000036-FU1 [091-051])
2-6-2004 (A)	IND	Type C Meeting Follow-up
2-6-2004 (B)	IND	Communication from Sepracor to FDA providing the list of Sepracor attendees for the Type C Meeting on February 9, 2004
2-10-2004	IND	Submission: IND Safety Reports: Follow-Up Report (MFR 2003SP000057-FU1[091-051]), Follow-Up Report (MFR 2004SP000013-FU1[091-060])

Date	Type	Activity
2-13-2004	IND	Submission: IND Safety Reports: Follow-Up Report (S012/R5093/CJW [091-051]),
2-19-2004	IND	Submission: IND Safety Reports: Initial Report (2004SP000025 [091-060]), Follow-Up Report (2004SP000011-FU1 [091-060])
2-20-2004	IND	Submission: IND Safety Reports: Follow-Up Report (2004SP000002-FU1 [091-026])
2-24-2004	IND	Protocol Amendment: Protocol 091-026, New Investigators (4)
2-25-2004	IND	Submission: IND Safety Reports: Initial Report (2004SP000027 [091-026]), Initial Report (2004SP000028 [091-060]), Follow-Up Report (2004SP000009-FU1 [091-060])
2-27-2004	IND	Official FDA Meeting Minutes from the Type C Meeting Between Sepracor and FDA on February 9, 2004
3-2-2004	IND	Submission: IND Safety Reports: Initial Report (2004SP000035 [091-060])
3-5-2004	IND	Submission: IND Safety Reports: Follow-Up Report (S026/R5385/JRW [091-051]),
3-11-2004	IND	Submission: IND Safety Reports: Initial Report (2004SP000038 [091-026])
3-17-2004	IND	Submission: IND Safety Reports: Initial Report (2004SP000041 [091-060])
3-18-2004	IND	Submission: IND Safety Reports: 1-Initial Report (2004SP000045) 2- Follow-up (2004SP000028)
3-24-2004	IND	Information Amendment: Pharmacology/ Toxicology
3-26-2004	IND	Submission: IND Safety Reports: Initial Report (2003SP000016-FU1 [091-060])
3-30-2004 (A)	IND	Communication from Sepracor to FDA providing a fax copy of IND Safety Reports: 7-Day Faxes: Initial Report (2004SP000054 [091-060]), Follow-Up Report (2004SP000011-FU2 [091-060])
3-30-2004 (B)	IND	Submission: IND Safety Reports: 7-Day Faxes: Initial Report (2004SP000054 [091-060]), Follow-Up Report (2004SP000011-FU2 [091-060])
3-31-2004	IND	Submission: IND Safety Reports: Initial Report (2004SP000050 [091-026]), Initial Report (2004SP000052 [091-051]), Follow-Up Report (2004SP000039-FU1 [091-026])
4-6-2004 (A)	IND	Protocol Amendment: Change in Protocol (Amendment No. 3, Protocol 4.0 [091-026])
4-6-2004 (B)	IND	Submission: IND Safety Reports: Initial Report (2004SP000056 [091-026])
4-8-2004	IND	Submission: IND Safety Reports: Initial Report (2004SP000057 [091-026])
4-13-2004	IND	Submission: IND Safety Reports: Initial Report (2004SP000061 [091-026])
4-16-2004	IND	Submission: IND Safety Reports: Initial Report (2004SP000069 [091-026])
4-20-2004	IND	Submission: IND Safety Reports: Follow-Up Report (2003SP000065-FU1 [091-060])
4-22-2004	IND	Submission: IND Safety Reports: Initial Report (2004SP000071 [091-060])
4-26-2004	IND	Submission: IND Safety Reports: Follow-Up (2004SP000050-FU1 [091-026])
5-3-2004	IND	Submission: IND Safety Reports: Follow-Up Report (2003SP000046-FU1 [091-051]), Follow-Up Report (2004SP000041-FU1 [091-060])
5-11-2004	IND	Submission: IND Safety Reports: Follow-Up (2004SP000017-FU1 [091-026])
5-13-2004	IND	Submission: IND Safety Reports: Follow-Up (2004SP000052-FU1 [091-051])

Date	Type	Activity
5-18-2004	IND	Submission: Resubmission of IND Safety Report (2004SP000052-FU1) to replace report submitted in Serial No. 306
5-20-2004 (A)	IND	Submission: IND Safety Report: Follow-Up Report (MFR 2004SP000069-FU1 [091-026])
5-20-2004 (B)	IND	General Correspondence: Type C Meeting Follow-Up
5-20-2004 (C)	IND	Communication from Sepracor to FDA providing a fax copy of Serial No. 309, General Correspondence: Type C Meeting Follow-Up
5-20-2004 (D)	IND	Communication from FDA to Sepracor providing reviewer comments on submission (General Correspondence: Type C Meeting Follow-Up) serial no. 309 dated 5/20/2004
5-25-2004	IND	Submission: IND Safety Report: Initial Report (MFR 2004SP000109 [091-051])
5-28-2004	IND	Communication from FDA to Sepracor granting request for Type C Meeting on JUNE 15, 2004
6-1-2004	IND	Submission: IND Safety Reports: Follow Up Reports (MFR 2004SP000051-FU1 [-060], 2004SP000011-FU3 [-060], 091051_030528_1 [-051])
6-3-2004 (A)	IND	Submission: IND Safety Reports: Initial Report (MFR 2004SP000116 [-060])
6-3-2004 (B)	IND	Several communications between 5/20/2004 and 6/3/2004: to notify FDA that a desk copy of the submission had been faxed to FDA to confirm FDA received the fax and to try to determine a teleconference time and date to schedule a teleconference time and date to try and finalize teleconference time and date to inform FDA of call number for teleconference and Sepracor list of attendees
6-7-2004	IND	Protocol Amendment: New Protocol, New Investigators (091-007), Protocol Synopsis (091-018)
6-10-2004	IND	Submission: IND Safety Report: Initial Report (MFR 2004SP000122 [091-060])
6-15-2004 (A)	IND	Communication from FDA to Sepracor regarding cancellation of June 15, 2004 teleconference
6-15-2004 (B)	IND	Submission: IND Safety Reports: Follow-Up Report (S091060_030330_1-FU2 [-060]), Follow-Up Report (SU091051_021125_1-FU5 [-051])
6-16-2004	IND	Submission: IND Safety Report: Follow-up Report (MFR. No. 2003SP000059-FU1) study 091-051
6-21-2004	IND	Submission: IND Safety Reports: Follow-Up Report (MFR 2004SP000061-FU1 [091-026]), Follow-Up Report (SU091051_030424_1-FU3 [091-051])
6-22-2004 (A)	IND	Submission: IND Safety Report: Follow-Up Report (MFR 2004SP000057-FU1 [091-026])
6-22-2004 (B)	IND	General Correspondence: Clarification of Information
6-25-2004	IND	Request by FDA for Feedback on Protocol 091-007 (submitted in Serial #313 on 07 June 04)
6-29-2004 (A)	IND	Information Amendment: CMC



Date	Type	Activity
6-29-2004 (B)	IND	Protocol Amendment: New Investigator (090-007)
7-6-2004 (A)	IND	Submission: IND Safety Report: Follow-up report (091-026) MFR. 2004SP000056-FU1
7-6-2004 (B)	IND	Submission: IND Safety Report: Follow-up report (091-060) MFR. 2004SP000045-FU1
7-12-2004 (A)	IND	Submission: IND Safety Report: Initial report (091-060) MFR. 2004SP000146
7-12-2004 (B)	IND	Submission: IND Safety Report: Follow-Up report (091-060) MFR. 2003SP000034-FU1
7-13-2004	IND	Submission: IND Safety Report: Follow-Up reports (091-060) MFR. 2003SP000014-FU1, 2004SP000013-FU2, 2004SP000016-FU1
7-14-2004	IND	Request by Sepracor for feedback on Protocol 091-007 (submitted in Serial #313 on 07 June 04)
7-15-2004	IND	Submission: IND Safety Reports: Follow-Up Reports (Unblinding of Study 091-051)
7-16-2004 (A)	IND	Submission: IND Safety Report: Follow-Up Reports (MFR SU091060_030619_1-FU2)
7-16-2004 (B)	IND	Submission: IND Annual Report (April 1, 2003 through March 31, 2004)
7-20-2004	IND	Communication from FDA to Sepracor providing Clinical Pharmacology and Biopharmaceutics comments regarding Protocol 091-007.
7-21-2004	IND	Submission: IND Safety Reports: Initial Report (MFR 2004SP000154 [-060]), Follow-Up Report (MFR 2004SP000146-FU1 [-060]), Follow-Up Report (MFR 2004SP000056-FU2)
7-23-2004	IND	General Correspondence: Authorization to Cross Reference IND 55,302
7-26-2004	IND	Protocol Amendment: New Protocol, New Investigators (2) 091-018
7-28-2004	IND	Submission: IND Safety Report: Follow-Up report (091-060) MFR. 2003SP000055-FU1
7-29-2004	IND	Submission: IND Safety Report: Follow-Up report (091-051) MFR. 2004SP000015-FU2
8-3-2004	IND	Submission: IND Safety Report: Initial Report (091-060) MFR. 2004SP0000167
8-6-2004	IND	Protocol Amendment: Change in Protocol (091-007)
8-12-2004	IND	Submission: IND Safety Report: Follow-Up report (091-060) MFR. 2004SP000154-FU1
8-16-2004	IND	Submission: Information Amendment: Pharmacology/Toxicology (4 Volumes)
8-24-2004	IND	Submission: IND Safety Report: Follow-Up report (091-060) MFR. 2004SP000009-FU2
9-2-2004	IND	Submission: IND Safety Report: Follow-Up report (091-060) MFR. 2004SP000025-FU1
9-14-2004	IND	Submission: IND Safety Reports: 11 Follow-up reports 091-026 unblinding
9-15-2004	IND	Submission: IND Safety Reports: Follow-up reports: 091-060 (MFR 2004SP000004 and 2004SP000167)
9-28-2004 (A)	IND	Submission: IND Safety Report: Follow-up report: 091-021 (MFR 2004SP000017FU3)

Date	Type	Activity
9-28-2004 (B)	IND	Communication from Sepracor to FDA regarding the change in the contact person for the CMC
10-4-2004	IND	IND Safety Report: Follow-up Report (MFR 2003SP000051) Study 091-060
10-14-2004	IND	Protocol Amendment: Revised forms FDA 1572 (2) for protocol 091-018
10-20-2004	IND	Submission: IND Safety Report: Initial Report (MFR 2004SP000219)
10-21-2004	IND	Information Amendment: Pharmacology/Toxicology (17 volumes)
10-28-2004	IND	Submission: IND Safety Report: Initial Report (MFR 2004SP000242)
11-2-2004	IND	Communication between Sepracor and FDA regarding submission of electronic SAS Datasets
11-3-2004	IND	Information Amendment: Pharmacology/Toxicology (20 volumes)
11-4-2004	IND	Submission: IND Safety Report: Follow-Up Report (MFR 2004SP0000045-FU2)
11-8-2004	IND	Submission: IND Safety Report: Follow-Up Report (MFR 2003SP0000008-FU2)
11-10-2004	IND	Submission: IND Safety Report: Follow-Up Report (MFR 2004SP0000242-FU1)
11-17-2004 (A)	IND	Submission: IND Safety Report: Follow-Up Report -060 (2004SP000035-FU1)
11-17-2004 (B)	IND	Information Amendment: Clinical (study 091-007)
11-17-2004 (C)	IND	Communication from Sepracor to FDA regarding the status of carcinogenicity report review and enrollment of 091-007
11-17-2004 (D)	IND	Communication from Sepracor to FDA providing a fax copy of submission Serial No. 354, Information Amendment: Clinical sent to FDA on this date
11-19-2004	IND	Protocol Amendment: Revised forms FDA 1572 for protocols 091-007, 091-060
12-02-2004	IND	Information Amendment: Pharmacology/Toxicology (3 volumes)
12-03 and 12-06-2004	IND	Communication from FDA to Sepracor regarding enrollment status of 091-007 and request by FDA for electronic carcinogenicity datasets
12-09-2004	NDA	General Correspondence: Type B Mtg - Pre-NDA Meeting Request by Sepracor to Review Arformoterol Clinical and Nonclinical Development Program
12-13-2004 (A)	NDA	Communication between Sepracor and FDA regarding the request for pre-NDA meeting
12-13-2004 (B)	NDA	Communication from Sepracor to FDA providing a copy of request for pre-NDA meeting
12-14-2004	IND	Information Amendment: Pharmacology/Toxicology
12-20-04 (A)	IND	IND Safety Report: Initial Report -060 (2004SP000313)
12-20-2004 (B)	NDA	Communication from FDA to Sepracor granting the meeting
12-21-2004	NDA	Communication between Sepracor and FDA regarding scheduling of the meeting
01-03-2005	NDA	General Correspondence: Request for CMC Pre-NDA Meeting (Type B)

Date	Type	Activity
1-4-2005 (A)	NDA	Communication between Sepracor and FDA regarding the pre-NDA meeting request (Serial No. 360)
1-4-2005 (B)	NDA	Communication from Sepracor to FDA providing request for CMC pre-NDA Meeting
1-11-2005	NDA	Communication from FDA to Sepracor regarding grant of the CMC pre-NDA meeting
1-12-2005	IND	Protocol Amendment: Revised forms FDA 1572 for protocol 091-007
1-12-2005 (A)	NDA	Communication from FDA to Sepracor providing a list of FDA attendees
1-12-2005 (B)	NDA	Communication from FDA to Sepracor regarding grant of the meeting, with a list of FDA attendees
1-20-2005	IND	Protocol Amendment: New Investigator (091-007) Amendment 1 and Revised Protocol Version 2.0 (091-018)
1-28-2005	NDA	General Correspondence: Type B Meeting Information Package
1-31-2005	NDA	General Correspondence: Type B (CMC) Meeting Information Package
2-1-2005	IND	Protocol Amendment: New Investigators (091-060)
2-11-2005	NDA	Communication from FDA to Sepracor regarding the CMC preNDA and the clinical/nonclinical preNDA meetings
2-28-2005 (A)	NDA	General Correspondence: Corrections to Type B Meeting Information Package
2-28-2005 (B)	NDA	Communication from Sepracor to FDA providing a fax copy of corrections to Type B Meeting Information Package
3-1-2005	IND	Communication from Sepracor to FDA regarding the change in the contact person for IND 55,302
3-4-2005 (A)	NDA	FDA requested Fax number for Ms. Elkins to send FDA responses to CMC PreNDA meeting questions
3-4-2005 (B)	NDA	FDA response to PreNDA meeting package questions (Clinical/Nonclinical)
3-4-2005 (C)	NDA	FDA response to PreNDA CMC meeting package questions
3-4-2005 (D)	NDA	FDA response to the PreNDA Clinical/Nonclinical meeting package
3-4-2005 (E)	NDA	Communication between Sepracor and FDA regarding clarification of question 1 and cancellation of the meeting
3-7-2005	NDA	Request by Sepracor for clarification on the response to Sepracor's Question 1 as presented in the CMC preNDA Meeting Package dated 1/31/2005
3-8-2005	NDA	FDA's response to Sepracor's request for clarification on Question 1 as presented in the CMC preNDA Meeting Package dated 1/31/2005
3-14-2005 (A)	IND	FDA request for information: Serial No. 349, dated 11-3-2004. – missing pages 3284-3482 be sent

Date	Type	Activity
3-14-2005 (B)	IND	Information Amendment Pharmacology/Toxicology Pages 3284-3423 of Serial #349
3-18-2005 (A)	IND	Information Amendment: Pharmacology/Toxicology
3-18-2005 (B)	NDA	General Correspondence: Sepracor Meeting Minutes (Clinical/Nonclinical PreNDA Meeting)
3-21-2005	NDA	Communication between Sepracor and FDA regarding the NDA number for Arformoterol Tartrate Inhalation Solution – the NDA number assigned is 21-912
3-28-2005	NDA	Official FDA Meeting Minutes from the March 7, 2005 Formoterol Pre-NDA (Clinical/Nonclinical) Meeting
3-29-2005	NDA	Communication between Sepracor and FDA regarding the requirements for paper desk copies of Volume 1 of the NDA for Arformoterol.
4-4-2005	IND	Protocol Amendment: New Protocol, New Investigator (091-019)
4-6-2005 (A)	NDA	Communication from Sepracor to FDA providing Sepracor's Proposals for Integrated Datasets for upcoming-NDA-for Arformoterol
4-6-2005 (B)	NDA	General Correspondence: Proposals for Integrated Datasets for upcoming NDA for Arformoterol
4-19-2005	NDA	Request by Sepracor for clarification of the post meeting note race and ethnicity discussion
4-22-2005	NDA	Communication between Sepracor and FDA regarding the date of ECAC meeting that had been discussed during the pre-NDA meeting
4-29-2005	IND	Information Amendment: Pharmacology/Toxicology
5-9-2005	IND	Protocol Amendment: New Investigators (091-019)
5-12-2005	IND	Final CAC Report for IND 55,302 (Response to carcinogenicity study review)
5-17-2005	IND	Follow-up Notice of Noncompliance – Site Management Organization Clinical Study 091-050
5-18-2005	NDA	General Correspondence: Proposal for inclusion of ECG waveform files from study 091-026 in the NDA
5-24-2005	IND	Email exchanges between Sepracor and the FDA regarding the submission timing of nonclinical reports to the IND
5-24-2005	NDA	General Correspondence Request for Clarification of E-CAC Minutes (FDA comments dated 5/12/2005 – concerning studies 090-833 and 090-828)
6-2-2005	IND	Protocol Amendment: New Investigators (091-019)
6-3-2005	NDA	Discussion between Sepracor and FDA regarding the status of the Data variability proposal for CRT datasets (submitted 4/6/2005), Desformoterol tox study (submitted 4/29/2005), ECG waveform dataset proposal (submitted 5/18/2005), and ECAC minutes clarification (submitted 5/24/2005)
6-10-2005 (A)	IND	Submission: IND Annual Report (April 1, 2004 through March 31, 2005)
6-10-2005 (B)	NDA	General Correspondence: Request for clarification of Clinical/Nonclinical Pre-NDA Meeting Minutes (information package on ethnicity)

Date	Type	Activity
6-17-2005 (A)	IND	FDA response to submission of 4/6/2005, serial number 371 General Correspondence: Proposals for Integrated Datasets for upcoming NDA for Arformoterol
6-17-2005 (B)	NDA	Follow-up communication regarding the status of the Ethnicity Submission sent to FDA on 6/10/2005 in response to the Pre-NDA meeting minutes
6-21-2005	NDA	FDA response to submission of 5/24/2005, serial number 375; General Correspondence Request for Clarification of E-CAC Minutes (FDA comments dated 5/12/2005 – concerning studies 090-833 and 090-828)
6-30-2005	NDA	General Correspondence: Request for Type A Meeting: Clarification of Pre-NDA Meeting Minutes
7-5-2005	NDA	Response to May 18, 2005, Serial Number 374 - General Correspondence: Proposal for Inclusion of ECG Waveform Files from Study 091-026 in the NDA Proposal for Inclusion of ECG Waveform Files from Study 091-026 in the NDA
7-7-2005 (A)	NDA	Protocol Amendment: Change in Protocol, New Investigators (091-019)
7-7-2005 (B)	NDA	Information Amendment: Pharmacology/Toxicology: Planned Procedures for Amendment to 2-Year Rat Carcinogenicity Study
7-7-2005 (C)	NDA	Teleconference between FDA and Sepracor regarding the grant of Type A Meeting (Teleconference) and meeting packages
7-11-2005	NDA	Letter from FDA granting the Type A Meeting (Teleconference)
7-18-2005	NDA	General Correspondence: Proposal for Content of Labeling in PDF Format
7-19-2005	NDA	FDA comments concerning Serial No. 381: Information Amendment: Pharmacology/Toxicology: Planned Procedures for Amendment to 2-Year Rat Carcinogenicity Study
7-22-2005	NDA	Request by Sepracor for a teleconference with the Pharm/Tox Reviewers at FDA to discuss the 2-year rat carcinogenicity study submitted on 7/7/2005 in serial no. 381
7-26-2005 (A)	NDA	General Correspondence: Type A Meeting Information Package
7-26-2005 (B)	NDA	Communication from Sepracor to FDA forwarding information for use during the teleconference with nonclinical FDA reviewers
7-27-2005	NDA	FDA response to Sepracor's fax of 7/25/05 concerning the upcoming teleconference to discuss the 2-year rat carcinogenicity study submitted on 7/7/2005 in serial no. 381
7-29-2005	NDA	Cancellation of the teleconference request made by Sepracor on 7/22/2005
8-10-2005 (A)	NDA	Communication between Sepracor and FDA regarding the teleconference to be held on Aug. 17, 2005. Follow-up on Serial No. 382 (request concurrence on submitting the label in PDF format not SPL format)
8-10-2005 (B)	NDA	Communication by FDA regarding rescheduling of teleconference
8-15-2005	NDA	Sepracor version of the minutes from the 8/15/2005 teleconference with FDA to discuss ethnicity issues
8-19-2005 (A)	NDA	FDA official meeting minutes from the August 15, 2005 teleconference to discuss ethnicity (reference back to 6/10/2005 submission and 3/7/2005 pre-NDA meeting submission)

Date	Type	Activity
8-19-2005 (B)	NDA	FDA response to submission of 7/18/2005 concerning SPL
9-8-2005	IND	Protocol Amendment: New Protocol (091-061), and IB. Information Amendment: CMC—Placebo for active comparator Foradil Aerolizer®
9-30-2005 (A)	NDA	General Correspondence: Proposed Proprietary Trade Name Expede™
9-30-2005 (B)	IND	Submission: 15-Day IND Safety Report: Initial Report (2005SP003031)
10-20-2005 through 10-27-2005	NDA	Communications between Sepracor and FDA regarding the process, principal point of contact, timeframe and payment ID number for Sepracor to pay the user fee for NDA 21-912 through the new FDA Web-based system
11-3-2005	IND	15-Day IND Safety Report: Follow-Up Report (2005SP003031)
11-7-2005	NDA	Communication between Sepracor and FDA regarding the status of the tradename submission (serial no. 385)
11-8-2005	NDA	Payment of NDA 21-912 user fee
11-10-2005	IND	Protocol Amendment: New Investigators (27) for 091-061
11-15-2005	NDA	Confirmation of payment of NDA 21-912 user fee
11-29-2005	NDA	Communication between Sepracor and FDA regarding an approximate date for submission of the NDA
12-8-2005 (A)	IND	Protocol Amendment: New Investigators (22) for 091-061
12-8-2005 (B)	NDA	<b>Original submission of eNDA for Arformoterol</b>
12-15-2005	NDA	Communication between Sepracor and FDA regarding the submission of eNDA and confirmation by FDA that the eNDA had been received on 12/12/05
12-16-2005	NDA	Communication from FDA to Sepracor to confirm that the NDA 21-912 had been received on 12/12/2005
12-20-2005 (A)	NDA	Communication from FDA to Sepracor requesting resubmission of eNDA which was not readable
12-20-2005 (B)	NDA	Communication regarding the unreadable DLT tape that contained the eNDA
12-20-2005 (C)	NDA	Communication from FDA regarding the available options for resubmission of the eNDA
12-20-2005 (D)	NDA	Resubmission of the Arformoterol eNDA - an exact copy of the original submission
12-21-2005	NDA	Communication between Sepracor and FDA regarding the resubmission of eNDA
12-28-2005 (A)	NDA	Communication from FDA to Sepracor providing a fax copy of the letter from FDA regarding the proposed trade name of EXPEDE
12-28-2005 (B)	NDA	Communication by FDA requesting second resubmission of the eNDA

Date	Type	Activity
1-3-2006 (A)	NDA	Communication between Sepracor and FDA regarding submission of additional trade names
1-3-2006 (B)	NDA	Communications between Sepracor and FDA regarding the status of eNDA
1-3-2006 (C)	NDA	A copy of the fax sent on 12/28/2005 requesting resubmission of the eNDA
1-3-2006 (D)	NDA	Communication from Sepracor to FDA regarding the status of the re-submission of the eNDA on 12/20/2005
1-3-2006 (E)	NDA	Communication from Sepracor to FDA regarding the cause of the defect in the tape
1-3-2006 (F)	NDA	Communication from Sepracor to FDA regarding second resubmission of eNDA
1-4-2006 (A)	NDA	Communication from Sepracor to FDA seeking confirmation of FDA's receipt of eNDA
1-4-2006 (B)	NDA	Communication between Sepracor and FDA regarding the status of the eNDA and the receipt/action date of the eNDA
1-4-2006 (C)	NDA	Communication between Sepracor and FDA regarding the status of the DVD copies of eNDA
1-4-2006 (D)	NDA	Request by FDA for third resubmission of eNDA - an exact copy of the original submission
1-5-2006 (A)	NDA	Discussion regarding the situation with the multiple resubmission of the eNDA
1-5-2006 (B)	NDA	Inquiry by Sepracor as to the issues with regard to the multiple resubmission of the eNDA
1-6-2006 (A)	NDA	Communication from Sepracor to FDA regarding the status of the latest eNDA submission
1-6-2006 (B)	NDA	Communication from Sepracor to FDA regarding the status of the latest eNDA submission
1-6-2006 (C)	NDA	Third resubmission of the Arformoterol eNDA - an exact copy of the original submission
1-6-2006 (D)	NDA	Cover letter for the 3rd re-submission of the Arformoterol eNDA
1-6-2006 (E)	NDA	Communication between Sepracor and FDA regarding the status of the eNDA and the NDA acknowledgement letter
1-9-2006 (A)	NDA	Communication between Sepracor and FDA regarding the status of the NDA acknowledgement letter
1-9-2006 (B)	NDA	Communication between Sepracor and FDA regarding the latest submission of eNDA
1-12-2006	IND	Protocol Amendment: New Investigators (Protocol 091-061)
1-13-2006	NDA	Continuing to seek the status of the NDA acknowledgement letter with no definite outcome
1-17-2006	NDA	Continuing to seek the status of the NDA acknowledgement letter with no definite outcome

Date	Type	Activity
1-18-2006	NDA	Request by Sepracor for the status of the NDA acknowledgement letter with no definite outcome
1-19-2006 (A)	NDA	Continuing to seek the status of the NDA acknowledgement letter with no definite outcome
1-19-2006 (B)	NDA	Continuing to seek the status of the NDA acknowledgement letter with no definite outcome
1-20-2006	NDA	Sepracor bringing the discussion to the next level at FDA, inquiring about the status of the NDA acknowledgement letter with no definite outcome
1-21-2006	NDA	Sepracor bringing the discussion to the next level at FDA, inquiring about the status of the NDA acknowledgement letter with no definite outcome
1-23-2006	NDA	Continuing to seek the status of the NDA acknowledgement letter with no outcome
1-24-2006 (A)	NDA	Discussions between Sepracor and FDA regarding the problems with the DLT tapes
1-24-2006 (B)	NDA	Sepracor continuing to seek the status of the NDA acknowledgement letter
1-25-2006 (A)	NDA	Sepracor continuing to seek the status of the acknowledgement letter for the NDA
1-25-2006 (B)	NDA	Communication between Sepracor and FDA regarding the status of the acknowledgement letter for the NDA
1-25-2006 (C)	NDA	Communication from FDA to Sepracor providing a fax copy of the acknowledgement letter for the Arformoterol eNDA
1-25-2006 (D)	NDA	Official acknowledgement of receipt letter from FDA for the Arformoterol eNDA - Date of Receipt is December 12, 2005
1-26-2006	NDA	Communication from FDA to Sepracor regarding Sepracor's receipt of the fax and cancellation of the scheduled meeting
1-27-2006	NDA	Communication between Sepracor and FDA regarding the problems with each of the DLT tapes that were submitted
2-1-2006 (A)	IND	Protocol Amendment: Change in Protocol, New Investigator (091-061)
2-1-2006 (B)	NDA	Communication from Sepracor to FDA regarding secure email set up
2-6-2006	NDA	Communication from FDA to Sepracor regarding the findings from testing the 3rd DLT tape sent to FDA
2-10-2006	NDA	Communication between Sepracor and FDA regarding the filing status and the 120 day safety update for Arformoterol
2-16-2006 (A)	IND	Protocol Amendment: Revised Forms FDA 1572 (091-019)
2-16-2006 (B)	NDA	Resubmission of two (2) sections (product.pdf and iss.pdf) of the Arformoterol eNDA that had originally been submitted to FDA on 12/8/2005 and again on 12/20/2005.



Date	Type	Activity
2-17-2006	NDA	Communication between Sepracor and FDA between 2/15/2006 and 2/17/2006 regarding: Status of the Tradename submission (Sepracor to FDA); Status of the 74 day letter (FDA to Sepracor); Updated Financial Disclosure Information (Sepracor to FDA); and ECAC comments (FDA to Sepracor)
2-23-2006 (A)	NDA	FDA informed Sepracor that the filing review is complete and the application is sufficient for review
2-23-2006 (B)	NDA	Communication by FDA informing the filing review is complete and the application is sufficient for review with a filing date of 2/10/2006
2-27-2006	IND	Submission: 15-Day IND Alert Report: Initial Report –061 (2006SP000798)
3-1-2006	IND	Submission: 15-Day IND Alert Report: Initial Report –061 (2006SP000853)
3-3-2006	IND	Submission: 15-Day IND Alert Report: Initial Report –061 (2006SP000799)
3-8-2006	IND	7-Day Fax Notification to precede 15-Day Alert Report
3-13-2006	NDA	Communication between Sepracor and FDA regarding the status of: Pharmacovigilance Proposal, NDA Status, Update on Trade Name Submission, and Pending ECAC Comments
3-14-2006	IND	Protocol Amendment: Revised Forms FDA 1572 (7 investigators) –091-061
3-15-2006	IND	Submission: 15-Day IND Alert Report: 1 initial, 1 follow-up (2006SP001060, 2006SP000853FU1). Note: MFR 2006SP001060 is an initial report that followed a 7-Day Alert Report Fax notification Sepracor sent to FDA on March 8, 2006.
3-21-2006	IND	Protocol Amendment: Revised Forms FDA 1571 Page 3's for Studies 091-012, 091-013, 091-014, 091-015, 091-016, 091-050
3-23-2006	NDA	Communication from FDA to Sepracor providing FDA's questions for nonclinical information in the NDA
3-29-2006 (A)	NDA	Submission by Sepracor of the response to the Division's request for information, as well as corresponding data files and SAS transport files
3-29-2006 (B)	NDA	Communication by Sepracor providing the status of the response to the nonclinical information response
3-30-2006	IND	Submission: 15-Day IND Alert Report: Initial Report, Follow-Up Report –061 (2006SP000798FU1, 2006SP001343)
3-31-2006	NDA	Amendment to a Pending Application: Submission of a Proprietary Trade Name - Brovana™
4-4-2006	NDA	Communication from FDA to Sepracor regarding: a problem encountered by one of the reviewers in opening the CMC product files; the trade name for Arformoterol and the mid cycle review meeting - May 2, 2006
4-7-2006	IND	Submission: 15-Day IND Alert Report: Initial Reports –061 (2006SP001399, 2006SP001493)
4-11-2006	NDA	General Correspondence: Amendment to a Pending Application: Request for Type C Meeting to discuss proposed pharmacovigilance plan
4-12-2006	IND	Protocol Amendment: New Investigator, Revised 1572's (091-061)
4-18-2006	NDA	Amendment: 120-Day Safety Update Report
4-19-2006 (A)	NDA	Communication from Sepracor to FDA informing the submission of the 120-Day Safety Update and inquiring about the request for the Type C Meeting

Date	Type	Activity
4-19-2006 (B)	NDA	Notification of electronic submission to CDER: Amendment to a pending application - 120-day Safety Update (also to notify the Field Office of the submission of the original NDA)
4-20-2006	IND	Submission: 15-Day IND Alert Report: Follow-Up Report –061 (2006SP001343FU1)
4-24-2006	NDA	Communication between Sepracor and FDA regarding confirmation of grant of Type C Meeting request
4-26-2006	NDA	Communication between Sepracor and FDA regarding the Rat carcinogenicity data sets in the NDA
4-27-2006	NDA	Amendment: (A2) Replacement of Nonclinical Toxicology Datasets from study 090-828A2
4-28-2006	IND	Submission: 15-Day IND Alert Report: Initial Report –061 (2006SP001746)
5-3-2006	NDA	Communication from FDA to Sepracor informing that no additional issues identified during FDA mid cycle review meeting
5-15-2006 (A)	NDA	General Correspondence: Briefing Document for Type C Meeting
5-15-2006 (B)	NDA	Communication from Sepracor to FDA regarding the status of the briefing document, trade name submission and the scheduling of GCP audits
5-17-2006	IND	Submission: IND Annual Report (April 1, 2005 – March 15, 2006)
5-18-2006	IND	Protocol Amendment: New Investigator, Revised Forms FDA 1572 (091-061)
5-19-2006	IND	Submission: 15-Day IND Alert Report: Initial Report –061 (2006SP002030)
5-25-2006	IND	Submission: 15-Day IND Alert Report: Initial Report –061 (2006SP002061) Follow-Up Report (2006SP001399FU1)
6-6-2006	IND	Submission: 15-Day IND Alert Report: Initial Report –061 Initial Report (2006SP002192)
6-7-2006 (A)	IND	Protocol Amendment: Change in Protocol, New Investigator, Revised Forms FDA 1572 (091-061)
6-7-2006 (B)	NDA	Communication from FDA to Sepracor providing review questions for CMC on the NDA regarding the Sterility Assurance Validation Report; Acceptance criteria for the environmental monitoring program; bacteriostasis/ fungistasis data used for validation of the use of the sterility test with the subject drug product
6-13-2006 (A)	IND	Submission: 15-Day IND Alert Report: Initial Report –061 Initial Report (2006SP002268), Follow-Up Report (2006SP001399FU2)
6-13-2006 (B)	NDA	Request for samples by FDA
6-15-2006	NDA	Email from Sepracor to FDA providing update on the two outstanding CMC requests
6-16-2006	NDA	FDA Response to questions in the May 15, 2006 Meeting Package regarding Pharmacovigilance Plan
6-19-2006 (A)	NDA	E-mails between Sepracor and FDA regarding FDA's request for samples
6-19-2006 (B)	NDA	Discussion of FDA's fax responses to the proposed Pharmacovigilance Plan
6-23-2006 (A)	IND	Submission: 15-Day IND Alert Report: Initial Report –061 Initial Report (2006SP002375), Follow-Up Report (2006SP001493FU1)

Date	Type	Activity
6-23-2006 (B)	NDA	Amendment: Response to FDA Request for Information to Evaluate the Sterility Assurance of the Drug Product
6-23-2006 (C)	NDA	Communication between Sepracor and FDA regarding the packaging of commercial vials
6-26-2006	NDA	Notification of electronic submission to CDER: Amendment to a Pending Application - Response to FDA Request for Information to Evaluate the Sterility Assurance of the Drug Product
6-27-2006 (A)	NDA	Review letter from FDA requesting additional information for the CMC reviewers on the NDA
6-27-2006 (B)	NDA	Fax of the letter from FDA requesting additional information for CMC reviewers on the NDA
6-27-2006 (C)	NDA	Arformoterol Tartrate Inhalation Solution Pharmacovigilance meeting Executive Summary, June 27, 2006
6-28-2006	IND	Submission: 15-Day IND Alert Report: Initial Report –061 Initial Report (2006SP002534), Follow-Up Report (2006SP002192FU1, 2268FU1)
6-29-2006	NDA	Communication from FDA to Sepracor regarding the status of the alternate trade name submission
7-10-2006	NDA	General Correspondence: FDA Request for Samples of Arformoterol
7-11-2006 (A)	NDA	Communication between Sepracor and FDA regarding the status of several submissions surrounding the Arformoterol NDA
7-11-2006 (B)	NDA	Fax copy of the official FDA meeting minutes from the meeting between Sepracor and FDA on June 27, 2006
7-12-2006 (A)	IND	Submission: 15-Day IND Alert Report: Follow-Up Report –061 (2006SP002534FU1)
7-12-2006 (B)	NDA	Amendment: Response to Chemistry Discipline Review Letter
7-12-2006 (C)	NDA	Notification of electronic submission to CDER: Amendment: Response to Chemistry Discipline Review Letter
7-13-2006 (A)	NDA	General Correspondence: Type C Meeting Follow Up (Pharmacovigilance Plan).
7-13-2006 (B)	NDA	Communication from Sepracor to FDA providing the cover letter from the arformoterol samples submission dated 7/10/2006
7-13-2006 (C)	NDA	Communication from Sepracor to FDA providing the follow up letter to the Pharmacovigilance meeting held on June 27, 2006 which was submitted to the NDA on 7/13/2006
7-19-2006 (A)	IND	Protocol Amendment: New Investigator, Revised Forms FDA 1572 (091-061)
7-19-2006 (B)	NDA	Communication from Sepracor to FDA regarding the status of the Trade name submissions for Arformoterol
7-21-2006	NDA	Amendment to a Pending Application: Submission of a Proprietary Trade Name - Arformex™
7-25-2006	NDA	Communication between Sepracor and FDA regarding the information request made by FDA regarding the pooled pivotal clinical trails 091-050 an 091-051

Date	Type	Activity
7-27-2006	NDA	Communication from FDA to Sepracor regarding the trade names and the submission of subsequent information on the asthma outline/synopsis discussed in the pharmacovigilance meeting 6/27/2006
8-3-2006 (A)	NDA	General Correspondence: Response to Clinical Request for Information
8-3-2006 (B)	NDA	Communication from Sepracor to FDA regarding the incoming General Correspondence: Response to Clinical Request for Information that was submitted to FDA on August 3, 2006
8-4-2006	IND	Submission: 15-Day IND Alert Report: Initial Report –061 (2006SP002771)
8-7-2006	NDA	Communication from FDA to Sepracor regarding the engraving on the vials
8-9-2006 (A)	IND	Submission: 15-Day IND Alert Report: Initial Report –061 (2006SP002838) Follow-Up Report (2006SP002192FU2)
8-9-2006 (B)	NDA	Communication from FDA to Sepracor regarding the annotated label in the NDA
8-16-2006	IND	Submission: 15-Day IND Alert Report: Initial Report –061 Follow-Up Reports (2006SP001060FU1, 2375FU1)
8-21-2006 (A)	IND	Submission: 15-Day IND Alert Report: Initial Report –061 Initial Report (2006SP002955), Follow-Up Report (2006SP002771FU1)
8-21-2006 (B)	IND	Protocol Amendment: New Investigators, Revised Forms FDA 1572 (091-061)
8-22-2006	NDA	FDA's response to an earlier e-mail by Sepracor regarding several issues in connection with the NDA (labeling/trade name/any outstanding issues)
8-28-2006	NDA	Communication from FDA to Sepracor providing CMC questions regarding the Response to the Chemistry Discipline Review Letter submission (7-12-2006)
8-29-2006	NDA	General Correspondence: Proposed Pediatric Asthma Plan
8-30-2006	IND	Submission: 15-Day IND Alert Report: Initial Report –061 Initial Report (2006SP003066), Follow-Up Reports (2006SP002268FU2, 2838FU1)
9-5-2006	IND	Submission: 15-Day IND Alert Report: Follow-Up Report –061 (2006SP001746FU1)
9-7-2006	IND	Submission: 15-Day IND Alert Report: Follow-Up Report –061 (2006SP002955FU1)
9-8-2006	NDA	Communication from Sepracor to FDA providing update on FDA's question regarding the actual embossing plan for Arformoterol vials
9-11-2006 (A)	NDA	Communication between Sepracor and FDA regarding regarding the timing of the response to the CMC information request will be sent in
9-11-2006 (B)	NDA	Communication from FDA to Sepracor regarding rescheduling of the date of the Labeling Teleconference
9-12-2006 (A)	IND	Submission: 15-Day IND Alert Report: Initial Report –061 Initial Report (2006SP003159, 3160), Follow-Up Report (2006SP002771FU2)
9-12-2006 (B)	NDA	FDA communication to Sepracor regarding proposed trade names
9-12-2006 (C)	NDA	Amendment to a Pending Application: Response to Chemistry Request for Information Letter dated 28 August 2006

Date	Type	Activity
9-12-2006 (D)	NDA	Notification of electronic submission to CDER: Response to Chemistry Request for Information Letter dated 28 August 2006
9-12-2006 (E)	NDA	Communication between Sepracor and FDA regarding CMC Information Request response documents
9-14-2006	NDA	Communication from FDA to Sepracor requesting results from <i>in vitro</i> characterization studies
9-15-2006	NDA	Communication between Sepracor and FDA regarding the timing of the CMC response ( <i>in vitro</i> characterization studies)
9-19-2006 (A)	NDA	Communication from FDA to Sepracor regarding FDA comments on draft labeling
9-19-2006 (B)	NDA	Communication from Sepracor to FDA acknowledging receipt of the e-mail and fax concerning draft labeling comments
9-19-2006 (C)	NDA	Communication from Sepracor to FDA with questions on the comments made by FDA on the labeling
9-20-2006 (A)	NDA	Communication between Sepracor and FDA regarding the CMC reviewer's questions
9-20-2006 (B)	NDA	General Correspondence: Response to FDA Request for CMC Information
9-21-2006 (A)	NDA	Response by FDA to questions from Sepracor regarding FDA's comments on draft labeling for Arformoterol
9-21-2006 (B)	NDA	Communication between Sepracor and FDA regarding the issues concerning trade name
9-22-2006 (A)	NDA	Communication from FDA to Sepracor regarding the final decision concerning the trade name situation
9-22-2006 (B)	NDA	Request by FDA for the revised PI
9-22-2006 (C)	NDA	Communication from Sepracor to FDA providing the medication guide and responses to the fax
9-22-2006 (D)	NDA	Communication from Sepracor to FDA providing the vial and foil for packaging
9-25-2006	NDA	Communication from Sepracor to FDA providing the revised carton file
9-26-2006	NDA	Sepracor version of the meeting minutes from the teleconference held between Sepracor and FDA on label negotiations. Communication between Sepracor and FDA regarding labeling issues and postmarketing issues
9-27-2006 (A)	IND	Submission: 15-Day IND Alert Report: Initial Report -061 (2006SP003265)
9-27-2006 (B)	NDA	Amendment to a Pending Application: Response to FDA Correspondence Regarding Proposed Labeling
9-28-2006 (A)	NDA	Response from FDA to Sepracor's submission of 9/27/2006 concerning labeling
9-28-2006 (B)	NDA	Communication from Sepracor to FDA regarding post marketing commitments from FDA

<b>Date</b>	<b>Type</b>	<b>Activity</b>
10-2-2006 (A)	NDA	Communication from FDA to Sepracor regarding the Post marketing study requirements
10-2-2006 (B)	NDA	Request by FDA for official submission to the NDA of the proposed labeling from 10/2/2006
10-3-2006 (A)	IND	Submission: 15-Day IND Alert Report: Follow-Up Report –061 (2006SP001746FU2)
10-3-2006 (B)	NDA	Communication from FDA to Sepracor regarding FDA responses to the labeling submitted on October 2, 2006
10-3-2006 (C)	NDA	Fax from FDA with responses to the labeling submitted by Sepracor on October 2, 2006
10-3-2006 (D)	NDA	Communication from Sepracor to FDA regarding the integration of the feedback from FDA into the draft PI
10-4-2006 (A)	NDA	General Correspondence: Proposal for Revised Draft Package Insert
10-4-2006 (B)	NDA	Communication from Sepracor to FDA regarding the revised labeling (package insert, medication guide, carton 30/60 count and pouch)
10-4-2006 (C)	NDA	Communication from Sepracor to FDA forwarding the 10/4/2006 version of the package insert-both clean and track changes along with the post marketing commitment letter
10-4-2006 (D)	NDA	Formal Submission of General Correspondence Letter previously e-mailed to FDA on 10/4/2006.
10-4-2006 (E)	NDA	Communication from FDA to Sepracor providing changes to the package insert
10-5-2006 (A)	NDA	Communication from Sepracor to FDA providing the 10/5/2006 version of the package insert-both clean and track changes
10-5-2006 (B)	NDA	Amendment to a Pending Application: Final Labeling
10-5-2006 (C)	NDA	Communication from Sepracor to FDA providing the revised PI with the changes requested by FDA
10-5-2006 (D)	NDA	The final package insert (clean and tracked changes versions)
10-6-2006	NDA	<b>FDA official letter to approve Brovana NDA and also the final printed labeling</b>